

DEPARTMENT OF ENERGY'S HUMAN
GENOME PROJECT ISSUES ARISING
FROM RESEARCH

Y 4. SCI 2:103/173

Department of Energy's Human Genome...

HEARING
BEFORE THE
SUBCOMMITTEE ON ENERGY
OF THE
COMMITTEE ON
SCIENCE, SPACE, AND TECHNOLOGY
HOUSE OF REPRESENTATIVES

ONE HUNDRED THIRD CONGRESS

SECOND SESSION

OCTOBER 4, 1994

[No. 173]

Printed for the use of the
Committee on Science, Space, and Technology



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DEPARTMENT OF ENERGY'S HUMAN GENOME PROJECT ISSUES ARISING FROM RESEARCH

TUESDAY, OCTOBER 4, 1994

HOUSE OF REPRESENTATIVES,
SUBCOMMITTEE ON ENERGY,
COMMITTEE ON SCIENCE, SPACE, AND TECHNOLOGY,
Washington, DC.

The subcommittee met, pursuant to call, at 1:40 p.m. in Room 2318, Rayburn House Office Building, Hon. Marilyn Lloyd (chairwoman of the subcommittee) presiding.

Mrs. LLOYD. The subcommittee will come to order. Good afternoon, ladies and gentlemen. I would like to ask unanimous consent that today's hearing be covered by the media. Without objection, Mr. Fawell, so ordered.

Today's hearing will explore the pivotal connections between research and its impact on society. Recent research has already found genetic links to a number of diseases such as Huntington's and cystic fibrosis. The recent discovery of the breast cancer gene indicates even greater opportunities for research to continue to understand and eventually treat a number of diseases.

As we achieve these impressive insights, we need to assure that the resulting information is handled with sensitivity and responsibility. The availability of this information for each individual raises a number of ethical, legal, and social issues that need to be addressed to maximize the research benefits to society and to minimize discrimination in access to employment, insurance, or social stigmatization.

Today's government and private sector witnesses will help us to understand the issues arising from research and frame appropriate mechanisms to deal with these very important emerging issues, and I would like to recognize my colleague, Mr. Fawell, for his opening remarks.

[The prepared opening statement of Marilyn Lloyd follows:]

**. THE HONORABLE MARILYN LLOYD
OPENING STATEMENT
OCTOBER 4, 1994**

**"HUMAN GENOME -- ISSUES
ARISING FROM RESEARCH"**

**GOOD AFTERNOON, LADIES AND GENTLEMEN, THE
SUBCOMMITTEE WILL COME TO ORDER. [I WOULD
LIKE TO ASK UNANIMOUS CONSENT THAT TODAY'S
HEARING BE COVERED BY THE MEDIA. WITHOUT
OBJECTION, SO ORDERED].**

**TODAY'S HEARING WILL EXPLORE THE PIVOTAL
CONNECTIONS BETWEEN RESEARCH AND ITS IMPACT
ON SOCIETY. RECENT RESEARCH PROGRAMS TO MAP
THE HUMAN GENOME AND UNDERSTAND THE GENETIC
LINK TO DISEASES HAVE ALREADY RESULTED IN
IMPROVED UNDERSTANDING FOR A NUMBER OF
GENETICALLY RELATED DISORDERS, SUCH AS**

HUNTINGTON'S DISEASE AND CYSTIC FIBROSIS.

THE ANNOUNCEMENT OF THE DISCOVERY OF THE BREAST CANCER GENE IS THE MOST RECENT SIGN THAT RESEARCH CAN PROVIDE KEY INFORMATION FOR PREDICTING PREDISPOSITION TO PARTICULAR DISEASES. THIS INFORMATION CAN ALSO HELP DEVELOP IMPROVED PREVENTIVE STRATEGIES AND THERAPIES TO DEAL MORE EFFECTIVELY WITH LIFE THREATENING DISEASES. THE IMPORTANCE OF THE RECENT DISCOVERY OF THE BREAST CANCER GENE IS THE FACT THAT EXPERTS THINK THAT ABOUT FIVE TO TEN PERCENT OF THE 180,000 BREAST CANCER CASES DIAGNOSED IN THE U.S. EACH YEAR ARE HEREDITARY.

THE HUMAN GENOME PROJECT WILL ENHANCE BOTH THE AMOUNT AND QUALITY OF GENETIC INFORMATION ON A NUMBER OF DISEASES, BUT THE USE OF SUCH INFORMATION MUST BE MADE WITH SENSITIVITY AND RESPONSIBILITY. FOR EXAMPLE, IN MANY DISEASES, GENETIC MAKE-UP MAY BE ONLY ONE FACTOR AMONG OTHER CAUSAL CONDITIONS THAT PREDISPOSE THE INDIVIDUAL TO DISEASE. LIKEWISE THE FACT THAT GENETIC INFORMATION MAY BE GATHERED FROM AN INDIVIDUAL WELL BEFORE ANY POTENTIAL OR EXPECTED ONSET OF THE DISEASE POSES A SIGNIFICANT DILEMMA REGARDING ITS USE.

ADDITIONALLY, THE FACT THAT OUR ABILITY TO PREDICT THE ONSET OF A DISEASE WITHOUT A

CORRESPONDING OR TIMELY CURE RAISES ISSUES ABOUT ITS USE BY THE POTENTIALLY AFFECTED INDIVIDUALS OR THE VARIETY OF CULTURAL, SOCIAL, AND ECONOMIC INSTITUTIONS IN OUR SOCIETY.

IN RECOGNITION OF THE SIGNIFICANT SOCIAL IMPACT THAT THE HUMAN GENOME PROJECT WILL HAVE, THE TWO MAIN FUNDING AGENCIES--THE NATIONAL INSTITUTES OF HEALTH AND THE DEPARTMENT OF ENERGY ESTABLISHED A JOINT WORKING GROUP TO IDENTIFY THE ETHICAL, LEGAL, AND SOCIAL ISSUES EMERGING FROM THE HUMAN GENOME PROJECT. THIS EFFORT OFFERS A UNIQUE OPPORTUNITY TO ANTICIPATE AND ADDRESS THE MYRIAD ISSUES IN A WAY THAT WILL MAXIMIZE THE BENEFITS OF GENOME RESEARCH TO SOCIETY AND

MINIMIZE DISCRIMINATION IN ACCESS TO EMPLOYMENT, INSURANCE, OR SOCIAL STIGMATIZATION.

OUR WITNESSES TODAY WILL HELP PROVIDE A NATIONAL FOCUS ON THE VALUE OF GENETICALLY RELATED RESEARCH. AT THE SAME TIME, THEIR COMMENTS WILL BE USEFUL IN ASSESSING CURRENT AND PROPOSED POLICY MECHANISMS TO DEAL WITH THE COMPLEX ISSUES COMING FROM THIS REMARKABLE BIOLOGICAL REVOLUTION IN OUR MIDST. THESE DELIBERATIONS WILL ALLOW US TO USE OUR SCIENCE IN A BENEFICIAL WAY AND MAINTAIN OUR CORE INDIVIDUAL RIGHTS AND VALUES AS A SOCIETY.

THIS HEARING RAISES BROAD SOCIAL ISSUES. I WANT TO COMMEND TINA VAN SICKLE OF THE SUBCOMMITTEE STAFF FOR BRINGING THIS COMPLEX AREA FORWARD IN A WAY THAT WILL HAVE MEANING AND FOCUS FOR DECISIONMAKERS. I ALSO WANT TO THANK LAURA BRICE OF THE UNIVERSITY OF MICHIGAN, WHO DURING HER INTERNSHIP AT THE SUBCOMMITTEE, PROVIDED A KEY ROLE IN LAYING THE FOUNDATION FOR THIS IMPORTANT HEARING.

Mr. FAWELL. Madam Chairman, I have a statement prepared, and I ask unanimous consent that it may be entered in the record, and then simply state that I agree wholeheartedly with the comments which you just stated, and I look forward to the comments. I am sure that I shall learn a great deal in this area.

Thank you very much.

[The prepared opening statement of Mr. Fawell follows:]

HONORABLE HARRIS W. FAWELL

OPENING STATEMENT

SUBCOMMITTEE ON ENERGY

HEARING

ON

"DEPARTMENT OF ENERGY'S HUMAN GENOME PROJECT —
ISSUES ARISING FROM RESEARCH"

October 4, 1994

The mapping of the human genome, the most ambitious undertaking in the history of biology, has the power to change our understanding of life at the basic level. But the ability to identify people who have or are carrying genetic diseases inevitably come before treatments are discovered. As a result, when all you can do is diagnose and you can't treat, each success in the gene-mapping project will create new ethical, legal and social implications—or ELSI in Government jargon.

Early on it was recognized that information arising from this research could be misused. And both DOE and the National Institutes of Health (NIH) are funding ELSI programs—with DOE spending about 3% or \$2 million annually, and NIH about 5%, or some \$5 million annually—to address these complicated ELSI issues. However, some of the ELSI efforts to date have been criticized as having the same cast of characters debating the same issues over and over again without moving toward the resolution of any of them.

I look forward to hearing from our witnesses today what these programs have produced in terms of concrete results, particularly in terms of general policy recommendations that Congress should consider in the near future.

Mrs. LLOYD. Thank you very much, and I do ask unanimous consent that all Members' opening statements be made a part of the record, and, Dr. Patrinos, if you would begin and we will go about 10 minutes, and then I think we will have to break for a vote. I am awfully sorry about our votes today.

STATEMENT OF DR. ARI PATRINOS, ACTING ASSOCIATE DIRECTOR, OFFICE OF HEALTH AND ENVIRONMENTAL RESEARCH, U.S. DEPARTMENT OF ENERGY, ACCOMPANIED BY DR. DAN DRELL, STAFF OF HUMAN GENOME PROGRAM

Dr. PATRINOS. Thank you, Madam Chairman. I am indeed honored to appear before your subcommittee this afternoon to testify on the human genome program and specifically on the associated activities of the Department of Energy. I have with me my colleague, Dr. Dan Drell, who is on the human genome program staff and who manages the part of our program that deals with the ethical, legal, and social issues.

I would like to start on a personal note, and I would like to say that I am honored to be appearing before you for what may be one of your last subcommittee hearings. I want you to know that I have followed your career for a number of years, starting back in 1975 and 1976 when I joined the Oak Ridge National Laboratory and you were at the time a freshman in Congress.

Mrs. LLOYD. And, Dr. Patrinos, that has been a long time ago and thank you for your leadership.

Dr. PATRINOS. Certainly speaking for myself, but also, I am sure, for many others at the Department of Energy, I can say that starting next January, we will miss your leadership and support, but we wish you the very best in whatever endeavors you have planned.

Mrs. LLOYD. Thank you very much.

Dr. PATRINOS. The Office of Health and Environmental Research is indeed very proud of its role in starting the human genome program back in 1986, in fact, the first government agency to commit to the mapping and sequencing of the 3 billion base pairs of the 24 chromosomes of the human genome. The DOE program sprung, in fact, from our longstanding research program of the health effects of energy production and use, including those of ionizing radiation.

Together with the NIH, the National Institutes of Health, the Department is pursuing this major undertaking that promises to revolutionize the fields of medical diagnosis and therapy. This program is also developing new applications in the broad field of biotechnology, including novel approaches to bioremediation, agricultural practices, and industrial processes.

The interagency coordination and cooperation with the National Institutes of Health is exemplary, starting with a Memorandum of Understanding in 1988 and a joint five-year plan in 1990 which was updated last year because of faster than predicted advances in new sequencing technologies, computational and data management procedures, and discoveries of disease genes.

Funding for the human genome program runs at approximately \$175 million per year with a DOE component at \$67 million, which is about 40 percent of the total. Our program is conducted at three genome centers at the laboratories Berkeley, Los Alamos, and Law-

rence Livermore, five other national laboratories, including Oak Ridge National Laboratory and Argonne National Laboratory, and also 53 universities and companies. We also have significant international partners in this effort. For example, England, France, Japan, Russia, and Canada.

The major focus for the DOE program has been on developing the tools for high-accuracy and high-speed sequencing and mapping and on the information and data infrastructure that is absolutely necessary for the success of such an ambitious program. The unique interdisciplinary and multidisciplinary capabilities of our national laboratories make them ideally suited for such tasks.

Our program also places a great emphasis on the ethical, legal, and social implications of human genome research that you spoke of. This effort, coordinated closely with the NIH and known as ELSI, commands approximately 3 percent of the program's budget, and the fund's research and development activities related to things such as privacy of personal genetic information, use of genetic information by employers in the workplace, commercialization of genome research results, and education of the general public or selected groups, for example, judges, in genetics.

The goal of ELSI is to stimulate public awareness of the important issues of the genome program and to provide the appropriate intellectual, social, and technical tools for informed policy making.

My written testimony contains many accomplishments of the technical part of our program, as well as many of the accomplishments and contributions of the ELSI effort.

Responding to the particular request of your invitation letter, I would like to note the study by the National Academy of Sciences Institute of Medicine on "Assessing Genetic Risk and the Implications for Health and Social Policy" which was published this year and the report on genetic information and health insurance issued by our ELSI working group last year.

Both reports identify many of the serious issues associated with genetic information and provide some policy recommendations. Regarding the National Bioethics Advisory Commission, which has been proposed by the Office of Science and Technology Policy, we certainly support its creation and its charter. Although the charter goes beyond human genome issues; for example, the broader issue of research involving human subjects, we will make sure that our ELSI working group and ELSI activities contribute to its functions and deliberations.

In conclusion, I would like to emphasize that the human genome program does not raise any novel ethical, legal, or social issues. Rather, it focuses attention on preexisting ones, such as the privacy of personal, medical, and genetic information, the implication of its use by third parties, such as employers and insurance, and the availability of predictive health information, particularly in the absence of immediate therapies.

All these issues will be with us regardless of the advent and advances of the human genome program. I believe, however, that only in these advances will we find the promise of effective and corrective medicine as well as a myriad of other solutions to problems facing us today.

This concludes my prepared remarks and I will be delighted to answer any questions.

[The prepared statement of Dr. Ari Patrinos follows:]

Statement of Ari Patrinos, Ph.D.

Acting Associate Director

Office of Health and Environmental Research

Office of Energy Research

U.S. Department of Energy

before the

Science, Space and Technology Committee

Subcommittee on Energy

United States House of Representatives

October 4, 1994

Madam Chairman and Members of the Subcommittee:

I am pleased to be here today to discuss the Human Genome Project, the nature and progress of the Department of Energy's (DOE) Biological and Environmental Research (BER) program's contributions to this project, and the key DOE activities conducted in this project under the Ethical, Legal, and Social Issues (ELSI) program. The Human Genome Project, initiated by DOE in the mid-1980's, is a truly international effort to develop and apply technology to map and sequence the human genome. It is one of the cornerstones of a dramatic technological change underway throughout the world that will impact many of America's most important industries. Beyond its obvious implications for medicine and human health, this project is creating technology and resources that will be applied to the characterization of the genomes of many living organisms. Such information will provide us with important new capabilities with applications in energy, environment, agriculture, materials, and industrial processes. The potential and appeal of this new targeted approach to biology can be seen in the recent establishment, around the world, of genome projects for several agricultural crops and animals. The Department, itself, has started a new program in FY 1994, called the Microbial Genome Initiative, targeted at characterizing the genomes of microbes of interest from an energy, environmental, or industrial perspective. Presently, more than a dozen countries, including England, France, Japan, Russia, Israel, and Canada are conducting organized Human Genome Research programs. This diversity of efforts has accelerated progress in the project; to date, the activities of international partners in human genome research have contributed significantly. As this hearing is going on, an international organization called the Human Genome Organization (HUGO) is holding a meeting here in Washington on recent advances in genome research.

In 1988, to enhance coordination between the National Institutes of Health (NIH) genome effort and the DOE genome effort, a memorandum of understanding was signed, in which NIH and DOE agreed to work together, coordinate their technical research and activities, share results, and contribute the respective strengths of each organization. In 1990, a five-year execution plan for the project was agreed to, with specific technical goals to be met in the areas of mapping and sequencing. Due to unexpectedly rapid progress and increased understanding in technical areas, such as genome mapping, the NIH and DOE revised these goals a year ago setting more concrete and ambitious milestones.

Research in the DOE Human Genome Program is conducted at the Genome Centers at Lawrence Berkeley Laboratory, Lawrence Livermore National Laboratory, and Los Alamos National Laboratory, other DOE National Laboratories (including Oak Ridge), more than 48 universities and companies, and in several other countries, e.g., Australia, Canada, Israel, and Russia.

The component parts of the program include:

Mapping: the development of more accurate genetic and physical maps of the human genome, that will establish the location of the genes in the human genome on the various chromosomes;

Sequencing: sequencing the human DNA, e.g. determining the exact sequence of the estimated three billion nucleotides on the 24 types of chromosomes in the human genome;

Databases: the development of various computerized databases so that the vast amount of information obtained can be efficiently analyzed and the different kinds of maps (genetic, physical, and DNA sequence-based) can be correlated;

Technology Development: to accomplish, more rapidly and cost effectively, the goals of mapping and sequencing the chromosomal DNA, and enable others to study more efficiently human genome organization and function;

Model Organisms: the study of selected model organisms so the wealth of information from other species, whose genomes are similar in organization or information content, can contribute to the more efficient characterization and understanding of the human genome;

Research Implications: a subprogram devoted to the study of ethical, legal, and social implications (ELSI) of genome research.

Activities of the Ethical, Legal, and Social Implications Program

It was recognized early in the development of the Human Genome Project that the knowledge to come from genome studies had broader medical and societal implications than those arising from other kinds of scientific knowledge.

This recognition was the basis for the establishment, both in the NIH and in the DOE genome programs, of subprograms devoted to ethical, legal, and social implications of genome research. Increases in genetic information about many individuals will eventually result from the Human Genome Project. One aim of the ELSI subprogram is to anticipate and address issues and implications that this new information will have for individuals and society. Another aim is to stimulate public awareness and discussion about the ethical, legal, and societal implications of genome research. In addition, ELSI studies should contribute to the identification and development of informed policy options that will address the ethical, legal, and societal impact of genetic information.

There is a very wide range of potential ELSI issues that needs to be considered. These range from the fair use of the large amount of genetic information that will be available as a result of the Human Genome Project, the impact of this information on genetic counseling and medical practice, impacts on personal reproductive decisions, impacts on the availability of health insurance and on employment practices, lessons from past uses and misuses of genetic information, privacy implications, even conceptual and philosophical implications, to implications of personal genetic variation. A very real, current example relates to the recent identification of the BRCA-1 breast cancer gene, that Mary-Claire King, a very important contributor to this work, may speak about in the next panel, and the association of forms of that gene with increased susceptibility to breast cancer. The availability of this new genetic information will, for many women, immediately raise the issue of whether they should be tested to determine their genetic susceptibility to

breast cancer. However, it appears that different forms of this gene exist that may each have a different effect on susceptibility to breast cancer. In addition, most breast cancers are currently thought not to be associated with inheritance of the BRCA-1 gene. Thus, the societal issues quickly become very complex. Under what circumstances should a woman be tested for the presence of a breast cancer susceptibility gene? Should she report the test results to her insurance company? Does she have obligations (legal or otherwise) to inform her employer? What actions are likely from her insurance company or employer if she does or doesn't report this information? Should she inform other members of her family of her test results? What professional obligations do physicians, nurses, or genetic counselors have to explain the implications of a test that is so new and for which the implications are yet so uncertain? What legal redress may exist, or should be contemplated, for discrimination against a woman who, now or in the near future, tests positive for a BRCA-1 version that predicts heightened susceptibility to a breast cancer and would, eventually, result in increased medical costs and work downtime? These are only some of the complex questions that are emerging as tests for a number conditions (e.g., cystic fibrosis, sickle cell anemia, Huntington's Disease, colon cancer, and, in the near future, breast cancer) are used or developed.

The DOE ELSI subprogram, which operates with three percent of the annual budget for the DOE Human Genome Program, or about \$2.0 million in FY 1995, elected to narrow its focus to issues of privacy and confidentiality of personal genetic information, genetic information privacy in the workplace, issues arising from commercialization and different approaches to intellectual

property protection of genetic information, studies on the implications of large DNA-based databases and data accumulations, and fostering genetic knowledge and literacy. In concert with the NIH ELSI program, DOE also supported a study, released last April, by the Institute of Medicine of the full range of ELSI issues with recommendations for informed policies.

One highly successful ELSI program was the DOE-supported development of educational curricula for high school students that was distributed to some 50,000 high school biology teachers. This curriculum is now being translated into Spanish and introduced into the Los Angeles school system. A "Primer on Molecular Genetics" produced in 1992 has been distributed to over 28,000 people and, on the Internet, has been accessed by over twice that number.

A project based at the University of Washington in Seattle introduces and involves high school students in the Human Genome Project by having them actually sequence short segments of human DNA. Their sequences become part of the sequence database for the entire project; these students both learn science by doing it and contribute to the eventual result.

The formulation of a "deskbook" reference work on genetics for members of the judiciary is another project. Judges are already seeing more and more DNA-based evidence in the context of various court cases. The Los Alamos National Laboratory has prepared and widely distributed an ELSI bibliography that has over 5,600 listings and which continues to grow.

DOE supported two Public Television documentaries about medicine and genetics

that were broadcast in 1993 and reached millions of viewers. DOE is supporting exhibits at both the San Francisco Exploratorium Museum and an exhibit ("Science in American Life") that recently opened in the Smithsonian's National Museum of American History.

The DOE ELSI program works very closely and cordially with the NIH ELSI program. Staff from the two programs are in frequent communication, attend each other's planning meetings and reviews as observers, have jointly sponsored workshops and meetings of the ELSI grantees, and both share the support and coordinate the functioning of the ELSI Working Group. This Working Group, currently chaired by Dr. Nancy Wexler of Columbia University, is now composed of 15 distinguished individuals from an extraordinarily broad range of backgrounds and expertise, and has existed since 1989 to coordinate the efforts by the DOE and NIH ELSI programs to avoid duplication of effort, to identify areas of research that need attention (often in anticipation of rapidly advancing science such as the discovery of the breast cancer susceptibility gene), and to periodically review the progress of ELSI grantees. The ELSI Working Group has also issued policy statements on various issues such as the applicability of the Americans with Disabilities Act to individuals with genetic conditions or increased susceptibility to a future medical condition (e.g., breast cancer), and on health insurance and genetic conditions.

Since the ELSI Working Group was a creation of the NIH and DOE Human Genome Programs, concern has been expressed about the relationship of this group to the scientific management of the genome programs as well as to the proposed

National Bioethics Advisory Commission (NBAC) recently proposed by the Office of Science and Technology Policy. The scientific managers of the DOE Human Genome Program strongly support the ELSI program and recognize its critical importance as an element of the overall Human Genome Project. The possible relation of the ELSI Working Group with the NBAC is difficult to determine at this time since this commission is not yet established. However, if the NBAC is formed, the outcomes of the DOE ELSI program would be freely furnished to the Commission; and the DOE genome program would look forward to cooperating with it fully. Since a charter for the NBAC has not yet been finalized, it is impossible to predict the impact of this Commission on DOE's ELSI program; however, it is our hope that the efforts of the NBAC and ELSI program will be complementary and not redundant.

Research and Development Activities of the DOE Human Genome Program

The scientific outcomes of the Human Genome Project will include (but are not necessarily limited to): novel technologies for the analysis of DNAs from other organisms; better understandings of the underlying causes of genetic diseases leading to more rapid, earlier, and more accurate diagnostic tests; better characterization of genetic susceptibilities to external agents and better accompanying risk assessments; studies of individual differences and insights into human evolution; and better understanding of biological functions and the developmental problems that can occur. All of this will lead to new approaches

to disease therapies, including gene therapies, new pharmaceuticals based on gene products, and new biotechnological industries.

The transfer of technologies developed in the Human Genome Project to the private sector continues to increase and the commercial interest in these technologies continues to grow. These technologies are transferred through a number of mechanisms including, Cooperative Research and Development Agreements, the Small Business Innovation Research Program, a DNA Diagnostics program of the National Institute of Standards and Technologies Advanced Technology Program of the Department of Commerce, and through independent investor funding. New investigations are also being started, using genome project technologies and scientific understanding, to explore the genomes of organisms that should be of interest for industrial and commercial uses. For example, DOE has started a Microbial Genome Initiative to take the first steps at characterizing the genomes of microbial species, many of which live in extreme environments and carry out biological processes of potential interest for purposes such as waste remediation, environmental cleanup, and other industrially valuable processes.

Recent accomplishments of the DOE Human Genome Program include the highest resolution physical maps of human chromosomes 16 and 19, based on work conducted at the Los Alamos National Laboratory by the group headed by Robert Moyzis and at the Lawrence Livermore National Laboratory, by the group headed by Anthony Carrano, respectively. The Chromosome 19 map contributed to the characterization of the genetic defect underlying the disease myotonic dystrophy, a common form of muscular dystrophy. Additional interest in

Chromosome 19 derives from the fact that this chromosome has several genes whose products are involved in the repair of damaged DNA. A DOE-supported researcher at the University of Washington in Seattle, Dr. Leroy Hood, has succeeded in sequencing nearly a million base pairs of DNA from the human and mouse genes that code for T cell receptor complexes. These genes code for molecules on the surface of certain white blood cells that are critically important for many immune responses to invading pathogens and are widely thought to be involved in protection against early tumor development. This successful DNA sequencing effort includes the longest continuous amount of human DNA that has yet been sequenced (about 620,000 bases) and made available through Genome Sequence Database (GSDB) to the entire scientific community. Additional accomplishments include advances in technologies that are speeding up DNA mapping and sequencing, novel "vectors" (laboratory tools critical for the manipulation of DNA in fragment sizes that can readily be characterized and studied), and improvements in various technologies and automation that are critically important to minimize the costs of sequencing and mapping.

Very recently, a genetic resource of cloned human DNA developed by a DOE-supported researcher, Dr. Melvin Simon at the California Institute of Technology, contributed to the identification of the previously mentioned BRCA-1 breast cancer susceptibility gene. Dr. Joe Gray, a researcher supported by DOE at the University of California, and his colleagues are improving a technology, called "comparative genomic hybridization", that allows rapid and sensitive comparisons of genetic material from different sources, including cancer cells and non-cancerous cells from the same individual. This technique could allow for rapid and routine tests for cancer

diagnosis, as well as facilitate the identification of new genes that when altered may lead to the development of cancer. In all these cases, it is the availability of the resources, technologies and new approaches from the genome program, taken altogether, that enables new, basic cutting-edge research and applications of that research.

One indication of advances in genome research within the last 10 years is the dramatic increase in new DNA sequence being added to publicly accessible sequence databases. In 1982, the longest continuous piece of DNA that had been sequenced was the genome of the small bacteriophage, lambda, 48,502 bases long. By 1992, the longest DNA sequenced was the third chromosome of brewers yeast, *S. cerevisiae*, 315,316 bases in length, a six-fold improvement. In 1994, with the sequencing of the entire third chromosome of the nematode worm *C. elegans*, totalling more than two million consecutive base pairs, there has been an increase of seven-fold in the length of continuous sequence in just two years and a 45-fold increase over the lambda sequence 12 years earlier. This rapid increase in sequencing efficiency means that vastly greater amounts of basic DNA sequence, and the biological and predictive information to be derived from it, will become available in the very near future.

These advances in sequencing rates underscore the importance of computerized databases for the storage and manipulation of genome research results. A particular focus of the DOE Human Genome Program is the development and use of computerized databases and the analytical tools necessary for the efficient searching of multiple, different data resources containing dispersed information about a particular gene. The rapid placement of data from genome

research into appropriate databases and the free international exchange of that data is crucial to the overall success of the genome program; this was considered so important from the beginning of the Human Genome Project that the 1988 memorandum of understanding between NIH and DOE underlying U.S. human genome-related research called on NIH and DOE to consider these issues in their joint management of the U.S. human genome program.

DOE is now the lead U.S. agency responsible for the operation and funding of the Genome Data Base (GDB) hosted at the Johns Hopkins University in Baltimore (NIH provides additional support as well). GDB is the worldwide repository for genome mapping data and exemplifies the worldwide databases of the future. While the main GDB central facility is located in Baltimore, an increasing number of international nodes have been established at locations around the world to facilitate more rapid access to GDB data. It appears to many that it is impractical for one site to have the expertise necessary to serve as the central repository for all the diverse types of genome and biological data that are becoming available; what is rapidly evolving instead is a "federated information infrastructure" that allows anyone at a remote site to link up, using his or her computer, to a global network of different data resources that are physically located on computers distributed around the world.

Identifying genes among raw DNA sequences is still a very large challenge (not unlike searching for a needle in a haystack except that the "needle" looks to a human like a piece of hay). One of the computer tools commonly used throughout the world for this type of search is "GRAIL", a program written by Dr. Ed Uberbacher and his colleagues at the Oak Ridge National Laboratory.

The use of this program through the Internet is free to anyone. DOE has also supported a DNA sequence database, called Genome Sequence Database (GSDB). GSDB was developed at Los Alamos National Laboratory (LANL) in the 1970s to provide DNA sequence information and resources to the research community. This project has recently been moved to the National Center for Genome Resources in Santa Fe, New Mexico. GSDB processes and stores DNA sequence information with a particular emphasis on serving the large scale sequence producers from the genome project, providing open access to that information with a standard database query language, and linking DNA sequence information with genome map information available in GDB. Research to develop better tools for data submission, for accuracy verification, for map representations, and for improved data access are also being pursued. The importance of this effort cannot be underestimated: to print the three billion "letters" of the human genome would require 100 telephone books, each of 1000 pages, and to find a particular bit of information in that amount of data would be impossible without dedicated computerized resources.

The development and transfer of novel technologies to other research laboratories and to the commercial sector are additional areas in which the DOE program has placed a major emphasis. Robots to automate the tedious process of building physical maps have been built and numerous laboratories have acquired this technology; the Lawrence Berkeley Laboratory in California has been a leader in building such robots and transferring them to other laboratories. Cooperative Research and Development Agreements (CRADAs) between National Laboratories and biotechnology companies have been established, among them a CRADA between Lawrence Livermore National Laboratory

and Perkin-Elmer to develop improved DNA sequencing technologies, and between Los Alamos National Laboratory and Life Technologies for single molecule sequencing. Mutation detection methodologies have also been developed. Valuable resources, such as libraries of highly purified DNA fragments from single chromosomes, have been made available to nearly every major mapping laboratory around the world through the National Laboratories Gene Library Project. A number of new startup, genomics-based biotechnology companies have also been established.

The great promise of the Human Genome Project is to build the information base and resources that will enable vast amounts of biological research and biotechnology applications well into the next century. The information, resources, tools, and computational capabilities will permit explorations of DNA function and malfunction, DNA damage from external agents and the accompanying risks to health, the elucidation of how biological function results from biological structure, the utilization of selected microorganisms or their gene products in extreme environments, and the development of a host of improved biotechnologies. These developments will contribute to better human health. Similarly, the technologies being developed from the Human Genome Project will continue to have enormous practical and economic impacts on agriculture, industry, energy production, environmental clean-up, and promote sustainable development. The continuing importance of ELSI studies is simply that each of us has a unique genome, and the unique information in our genomes both identifies us and has predictive implications for our future health. None of us has an "ideal" or "perfect" genome (even if such a concept could be defined.) Most individuals carry genes that would have serious

consequences for health if they were not masked by other genes. How we handle this greater amount of information from current human genome research will present challenges to us at many levels.

This concludes my prepared testimony. I would be happy to answer your questions.

ARI PATRINOS

Ari Patrinos received a Diploma in Mechanical and Electrical Engineering from the National Technical University in Athens, Greece, in 1970. He served as a teaching assistant in fluid mechanics during the period 1968-1970 and during that time he was also a summer student research assistant at the British Petroleum research facility in Sudbury-on-Thames, England. He came to the U.S. in 1970 and entered the Graduate School of Northwestern University, in Evanston, Illinois, as a Walter P. Fellow. He received his Ph.D. in mechanical engineering and astronautical sciences in 1975 and the subject of his dissertation was "A Numerical Study of the Chicago Lake Breeze." His graduate research also included experimental studies in low speed wind tunnels. For the period 1973-1975 he also consulted for Argonne National Laboratory on problems involving numerical solution of reactor system flows.

Dr. Patrinos was an Assistant Professor at the Mechanical and Aerospace Sciences Department at the University of Rochester during the period 1975-1976 where he taught and conducted research on computational fluid mechanics, hydrodynamic stability and experimental methods. He joined Oak Ridge National Laboratory in 1976 to conduct research on weather and climate modification caused by large power generating systems. He led a team of interdisciplinary scientists on a series of field programs around large power plants and developed statistical techniques for climatological analyses. He also worked on numerical codes for loss-of-coolant (LOC) nuclear accident simulations as well as for river flows and lake circulations.

In 1980, Dr. Patrinos joined Brookhaven National Laboratory where he developed numerical models for atmospheric processes involved in the acidic deposition phenomenon. He also led several field programs in and around major cities (Philadelphia and Washington, DC) to determine the impacts of their emissions on local pollution deposition. In 1984, he was detailed to EPA and to the National Acid Deposition Assessment Program (NAPAP) staff in Washington, DC, and worked on scientific assessments. He also collaborated with NASA Langley in the development of models simulating the acidic deposition phenomenon on regional scales. He joined DOE as a detailee in 1986 and worked on the restructuring of DOE's atmospheric sciences program. He became a public servant in 1988 and led the expanded DOE research effort in global change. He was the director of the Atmospheric and Climate Research Division (ACRD) of DOE's Office of Health and Environmental Research (OHER) until 1990. ACRD was then merged with OHER's Ecological Research Division and he became director of the combined Environmental Sciences Division.

Dr. Patrinos represents DOE on several subcommittees of the Committee on Environment and Natural Resources and is the Chairman of the Processes Working Group of the U.S. Global Change Research Program. He has also represented DOE at a number of Congressional hearings and functions as well as at international fora.

Dr. Patrinos has published widely in the fields of computational fluid mechanics, atmospheric flows, atmospheric chemistry, and climatology. He is a member of the American Society of Mechanical Engineers, the American Geophysical Union, the American Meteorological Society, and the Greek Technical Society.

Mrs. LLOYD. Thank you very much.

I apologize. We are going to have to break for a vote and we will be right back. I would like to acknowledge the presence of our Chairman, the Honorable George Brown, and we certainly appreciate you being with us and we will look forward to hearing from you when we return.

[Recess.]

Mrs. LLOYD. We will resume our hearings and certainly I do want to recognize our distinguished Chairman of the full committee, the Honorable George Brown, who has done such an outstanding job with the leadership of the full committee.

Mr. Chairman.

Mr. BROWN. Thank you very much, Madam Chair. We have a lot of questions that the committee would like to have you answer.

Is that Dr. Drell out there? How are you, Dr. Drell?

Dr. DRELL. Nice to see you.

Mr. BROWN. And I would just like to have one or both of you describe for me the problems and the opportunities arising out of the rather complex way in which we have organized the human genome project.

It has leadership from DOE and from NIH. It is an international program. It has coordination at the White House level. The question I have to ask myself, is this system functioning well? Is it getting results? If there are problems, what are they? We may take this as a study in organizational management as much as a research problem in biochemistry.

Dr. PATRINOS. I would be delighted to answer, Congressman Brown. The human genome program is perhaps one of the best coordinated research efforts in the Federal Government. It is, in fact, the paradigm for interagency collaboration.

The involvement of both agencies, the National Institutes of Health and the Department of Energy, from the very beginning, back in the late 1980s, started essentially with a series of working groups that looked at all aspects of the human genome program from sequencing to mapping to the informatics, to the ethical, legal and social issues, sorted out the territory for research in a very collegial way, shared information, and as I mentioned in my introductory remarks, signed a Memorandum of Understanding at the very early stages of the program and jointly issued a five-year research plan, which last year was updated because of the significant advances, much more than anticipated in the early days, progress dealing with sequencing and mapping and informatics.

The collaboration also at the international level is very well done. Organizations such as the Human Genome Organization, known as HUGO, coordinates many aspects of the effort, and I also would like to say that the community involved in the human genome program is rather small, despite its prominence and the attention it gets.

So at the scientist level, also coordination is excellent, and with the advent of electronic communications, for example, scientists and science managers are in touch almost in real time and continuously.

Mr. BROWN. Would you consider that that ability to be in almost—in touch in almost real time to be a significant factor in the quality of the coordination that takes place?

Dr. PATRINOS. Absolutely, Mr. Chairman. Absolutely.

Mr. BROWN. You see, I have had the opportunity to be intimately involved with the organization of complex projects at the Federal level for 30 years, and I have studied intensively the problems in the period for the previous 20 years before that, and there was always a struggle between agencies. A classic one is between the Department of Agriculture and the Department of NIH on just how to conduct human nutrition studies. They never really got their act together and that is far less complex than this.

I am willing to accept in good faith what you tell me, but I would feel better if you would reveal to me that there is a little bit of tension here occasionally.

Dr. PATRINOS. I would be glad to do that. Certainly I think there is tension, but the tension is what I would consider very healthy. It represents different cultures, scientific and research cultures and technological cultures, and they both—in this case, the NIH and the DOE—bring in their individual strengths and nuances to the program that further enriches it and makes it much more vibrant. It is essentially greater than the sum of the individual parts.

I mentioned, for example, the strength that the Department brings through its national laboratories, the multidisciplinary and interdisciplinary teams that can be brought to bear on a problem such as the sequencing, which requires a lot of repetitive activities, for example, where the laboratories are ideally situated to do it, whereas the NIH is obviously much better in the disease-hunting activity. So that marriage of capabilities and backgrounds makes it a strong program.

Mr. BROWN. I will confess to you, I haven't read the Memorandum of Understanding. Does it attempt to clarify distinctions as to the roles of the two agencies based upon some areas of expertise or some other way in which you can say this is my part of the pie and this is your part of the pie?

Dr. PATRINOS. I will let my colleague, Dan, who is more familiar with the Memorandum respond to you, Congressman.

Dr. DRELL. It is a pleasure to be here, first of all. Thank you very much. That Memorandum of Understanding was done in 1988 and a lot has happened since then. At the time, only in the broadest terms were areas of, for want of a better word, turf defined there, and so much has happened since then that I think it is hard to go back to that MOU and its exact language.

Mr. BROWN. Well, I won't belabor this point, but I am interested in following this. If it truly is a paradigm for organization of complex projects, I got a lot more complex projects I want to apply that paradigm to.

I thank you, Madam Chair.

Mrs. LLOYD. Thank you very much, Mr. Brown.

Mr. Fawell.

Mr. FAWELL. Thank you, Madam Chairman.

I did fully read your statement last night. It was interesting reading. When I said I know I would learn a lot from this hearing, it is because I start with not that much knowledge, but I refer you

to page 4 of your statement, and you refer there to the very wide range of potential ELSI issues, and there is quite a wide range that you set forth, but you also make references to lessons from past uses and misuses of genetic information.

Could you elucidate a bit on that? Where have we stumbled and fallen and learned lessons from the past? Not too great a past, I gather, that we are referring to.

Dr. PATRINOS. No, it isn't, and I will also allow Dr. Drell to respond.

Dr. DRELL. A lot of medical information has a genetic component. That has become a lot clearer in recent years as our tools for analyzing the genome and its parts have improved. What that phrase refers to is the fact that—well, two things really, but one is, and I can give you one just extreme example as a case study.

In the early 1930s in Germany, some pretty horrific things were done, in part based on perceived genetic and—well, largely genetic differences between peoples. It was felt back then that the Jews were genetically different and something pretty extreme had to be done about that. We, of course, are horrified by that example ever since.

We don't view with calm the idea of genetics being used to discriminate between people based on something over which someone has no control, and that is one of the explicit aims of the ELSI program at both agencies is to try and avoid that.

Mr. FAWELL. Is there—I imagine there are a number of groups that have publicly organized and resist this kind of research on the assumption that it can lead to an uncontrollable kind of science.

Do I make myself clear?

Dr. PATRINOS. We have not really experienced any such opposition in all the various activities associated with this program. We have done a—we believe, a very thorough job educating the public and policy-makers on what can and cannot be expected as a result of this research, and I think the reaction we are getting from the public has been a very, very positive one.

The biology curricula that we developed with emphasis on the genome program that is now, in fact, being translated into Spanish and introduced into the Los Angeles school system, the use of the primer on human genetics that is now in the INTERNET, for example, and accessed by many thousands of people, I think the concerted effort that this program is making to educate, not just the scientists and the policy-makers, but the general public, has had a very positive effect and has avoided the type of problem you have alluded to. We have not experienced any such reaction.

Mr. FAWELL. I may be mixing up science here, but in a trip I made several years back, there were some references to genetic engineering that would allow, for lack of any better phraseology than this layman can come up with, microbes that could aid in waste cleanup, things of this sort by genetic changes. Is that—or am I mixing this up with some other endeavors?

Dr. PATRINOS. I don't think you are mixing it up, but you are referring to one of the applications of the human genome program or the microbial genome initiative, in fact, that we have also launched this last year, the ultimate application of the knowledge and the

technology that we developed in the course of this particular program.

And naturally the issue that you raised about introducing genetically-engineered microorganisms for a variety of applications is something that needs to be deliberated and debated.

ELSI is in fact one of the mechanisms that does just that, and also the new Bioethics Advisory Commission that the White House plans to introduce.

I think only in the deliberation and the debate can we sort some of those issues, but I don't consider that there is a massive opposition to some of those applications. There may be some questions and some doubts, but they need to be addressed, debated, and deliberated.

Mr. FAWELL. Are there some areas of genetic research at this time that an entity interested in the ethical aspect may be closely watching, overseeing, indeed, recognizing that the potential of public misunderstanding or otherwise engendering some public resistance might come more so in one area than another?

In your statement, you referred to certain worms being basically changed genetically, and I assume if they are changed genetically, maybe they will do something that is quite helpful to science, et cetera, et cetera.

So are you taking special areas and saying, we do want to keep abreast of what is happening here?

Dr. PATRINOS. Absolutely, we should keep abreast, particularly those aspects that deal with human genetics and the possible misuses, like Dr. Drell referred to, whether it is for insurance reasons or for employment reasons. These are issues that need to be watched very, very carefully.

Mr. FAWELL. What about genetic changes that may cause—

Dr. PATRINOS. Those as well. They are issues that are in the agenda, so to speak, of the ELSI activities, yes.

Mr. FAWELL. Well, I thank you very much. There is much I need to better understand all of this, but it is immensely interesting and I thank you for your testimony.

Dr. PATRINOS. My pleasure.

Mrs. LLOYD. Thank you very much, Mr. Fawell. At this point, we are going to break the hearing for about one minute because our photographer is here, and Mr. Fawell and I would like some pictures with our distinguished witnesses this afternoon. So we ask for the indulgence of the audience.

[Off the record.]

Mrs. LLOYD. Dr. Patrinos, I am sure you are aware this is the second hearing on human genome issues that we have called, and our attention really surfaced on the moral and ethical and the legal questions as a result of the fallout on the research and development technologies that were used in our nuclear medicine advances, and I for one am alive because of advances in nuclear medicine.

I am sure that I am not the only one in this room that we have been touched with the good things that have happened, and it seems to me that I wanted to make sure that we didn't find ourselves 20 years from now involved in some similar controversy as

a result of the good work that you are doing in this field of research.

It seems to me that the world community will certainly make the determination of how far that we will go in this very valuable research that will not only increase the quality of life, but the expectancy of life-span as well.

To what extent is DOE encouraging meetings, seminars to really let the American people know what we are trying to do, to stimulate the type of thoughtful public debate instead of a hysterical or emotional response? This is what I hope is not happening.

Dr. PATRINOS. As I mentioned earlier in my remarks in answer to Congressman Brown, this is one of the programs that is a paradigm for interagency collaboration, as well as integration in the scientific community and with the general public, the investments we have made in education, whereas the example such as the curricula that we have developed, the public meetings that we have sponsored—

Mrs. LLOYD. I was referring to the public participation, the public participation in the seminars so there would be an understanding not only interagency, but with the taxpayers.

Dr. PATRINOS. Very much so. There is a very strong public component, primarily because of the ELSI angle, and this program in many respects was a pioneer because it anticipated the ethical, legal, and social issues that were associated with human genetics and the mapping of the human genome, and consequently, before it even, I would say, sequenced the very first base pair, dealt with the issue of information and communication to the public, of building essentially the public's support, so that when this program was—finally took off in terms of advances and in terms of application, the field was fertile for a better understanding and a better convincing of the public of the value of the program and of its potential contributions.

Mrs. LLOYD. Dr. Drell, would you like to comment?

Dr. DRELL. I would just cite a couple of things that our ELSI program has done towards what you raised. We have sponsored for several years a series of seminars at the Cold Spring Harbor Laboratories DNA Learning Center expressly for public policy-makers. I know several members of the staffs of some House and Senate Members have attended those seminars to be introduced in a sympathetic way to what DNA is and how one studies it.

We have contributed, along with a number of other agencies, and I expressly include NIH in this, to some public TV documentaries that have been broadcast. Dr. Patrinos mentioned the high school curriculum. If you want to have impact, high school is a good place to have it. That curriculum has been mailed to some 50,000 biology teachers, and we are getting a variety of reports back on its use and effectiveness.

This is—I would only say one more thing, which is, this is an area of enormous importance to us and we devote a fair amount of our ELSI efforts to it. It is just too important not to.

Mrs. LLOYD. Thank you very much. You mentioned that—and I agree with you. Certainly our DOE labs are the perfect foundation to do the kind of research that you are doing, and I just couldn't agree with you more.

How do we involve the labs? Do you base it on what you anticipate their experience could be or their past experience, or how do you decide on the allocation of tasks and funding in this work?

Dr. PATRINOS. As you have referred to in—earlier, Madam Chairman, the national laboratories and the Department of Energy has been involved in the studies of health effects of energy production and use, including ionizing radiation for many, many years, in fact, decades. In fact, that is where the whole field of nuclear medicine sprang from.

So the national laboratories had excellent biology core competencies, I would say, to use the vernacular of our current system. So consequently, those core competencies were applied immediately to the challenges of the human genome program because of the existence of the multidisciplinary and interdisciplinary team at the laboratories, the computing infrastructure that helped enviroinformatics, the biology development that became imperative for improvements in sequencing and mapping. It was just a natural match.

We also made sure that the science that was pursued at the national laboratories in mapping and sequencing and associated studies was peer reviewed to the highest possible standards. We instituted competitive procedures so that the very best scientists in the labs were the ones that ended up being funded to pursue this research, and we are very, very proud of the high quality and the peer reviewable activities that we have instituted in the labs to make sure that it essentially did the job in the most cost-effective fashion.

Mrs. LLOYD. So you are not only targeted on labs, but you target in on the individual scientist as well?

Dr. PATRINOS. Absolutely. Very much so.

Mrs. LLOYD. That is very good. How much do you believe that scientists should be involved in understanding the societal impacts of their research and how should they be involved with looking at the ramifications of genetic research?

Dr. PATRINOS. To me there is really not a significant difference between a scientist and a bioethicist. In fact, I would argue that most scientists are bioethicists, just as bioethicists are scientists. So I am very much for a broad participation of both scientists, practicing scientists and lay public representatives in the deliberations and debates associated with the ELSI issues.

I would want to see the scientists very actively involved in dealing with these perhaps thorny issues associated with the ethical, legal, and social implications of the human genome program.

Mrs. LLOYD. You indicated that these issues become very complex and we are going to have to find answers.

How do we go about developing our answers?

Dr. PATRINOS. The answers to many of the ethical, legal, and social problems can only be arrived at through active deliberation and debate in bodies such as the ELSI working group that we have and the National Bioethics Advisory Commission that the White House is proposing.

It is also arrived at through groups like the National Academy of Science, for example, that dealt with the issue of implications for

health and social policy of genetic risk. I guess my answer is through debate, deliberation, and hard work.

Mrs. LLOYD. Do you see us—do you anticipate any problems that we can't fix? Are we getting into areas where we are going to have problems with discrimination, with insurance and employment?

Dr. PATRINOS. There are potential problems, but they are not insurmountable problems, and, as I mentioned earlier, they are problems that are with us and will be with us regardless of what we have done in the human genome program.

They deal with medical genetic records. Even if we didn't have the human genome program, we would be wrestling with these problems anyway.

However, the human genome program is the one that offers at least some hope that we will be able to realistically arrive at some of the solutions to these very thorny problems in terms of cures and prevention.

Mrs. LLOYD. I don't think that I have personally arrived at a straight road in my own philosophy. As a researcher, I know that I want you to continue, I want you to continue doing the good work that you are doing, but somewhere along the line, when do we say that, how much is it going to affect an individual's life?

For instance, in breast cancer, Dr. King is going to discuss with us a little bit later on, how do you say, well, I don't think it is really going to affect you? Or does somebody have to carry the mantle around the rest of their life that they could be a potential victim? It is troubling to me.

Dr. PATRINOS. I agree that this is a very tough problem, and it does raise some serious questions that we will have to deal with and deal with very quickly as we discover more and more disease genes, particularly for diseases that we can offer very little hope in terms of cures.

I admit that this is an issue that is a thorny one and needs to be debated and discussed and dealt with somehow. I am not belittling its importance or its potential complication. It is just that I don't see any alternative to pursuing full speed ahead in terms of the objectives and the goals of the human genome program, because in its success lies the promise of some solution.

Mrs. LLOYD. Great breakthroughs for a better life.

Dr. Drell, do you have further comments?

Dr. DRELL. I was just going to extend a point that Dr. Patrinos made about scientists and bioethicists. Some of these issues require some technical understanding and input, and that to me is a very strong guide, that the scientists who are part of the genome program and the, I hate the term, but I am going to use it anyway, the ELSI types who are also part of the genome program have to talk, communicate, converse, and work together, otherwise whatever emerges from the program is just not going to be as robust as we would like it to be.

And also some of the problems that we are talking about go far beyond any one community, and so the research on them and the admittedly very complex process of responding to them has to be an inclusive one far beyond what the people currently considered part of the genome program.

Mrs. LLOYD. I thank you very much, and I would like to recognize Mr. Ehlers for any comments he might have at this time.

Mr. EHLERS. None at this time. Thank you.

Mrs. LLOYD. We will be submitting additional questions in writing for you for the record for this hearing. In the interest of time, so that I can hear from all the other witnesses, I want to thank you so very much and I wish you both well. Thank you very much.

We would at this time like to welcome Dr. Mary-Claire King, Professor of Genetics at the University of California in Berkeley, Dr. Neil Holtzman, Johns Hopkins Medical Institutions, Dr. Ellen Wright Clayton, Assistant Professor of Pediatrics and of Law at Vanderbilt University, Dr. Robyn Nishimi, Senior Associate at the U.S. Office of Technology Assessment here in Washington.

We will listen to all of your testimony before we begin our questioning. So, again, I look forward to hearing from all of you. I want to thank you for being here and extend to you a warm welcome.

Dr. King.

STATEMENTS OF DR. MARY-CLAIRE KING, UNIVERSITY OF CALIFORNIA, BERKELEY, CA; DR. NEIL HOLTZMAN, M.D., M.P.H., JOHNS HOPKINS MEDICAL INSTITUTIONS, BALTIMORE, MD; DR. ELLEN WRIGHT CLAYTON, ASSISTANT PROFESSOR OF PEDIATRICS AND OF LAW, VANDERBILT UNIVERSITY, NASHVILLE, TN; AND DR. ROBYN NISHIMI, SENIOR ASSOCIATE, OFFICE OF TECHNOLOGY ASSESSMENT, WASHINGTON, DC

Dr. KING. Thank you very much, Mrs. Lloyd. It is an honor, almost beyond even my power to come up with words to tell you what a pleasure it is to appear before your committee, and indeed to appear before you who have been so supportive of this research from the beginning.

I would like to spend a very few minutes telling you a little bit about the history of the search for genes that influence high risks of breast cancer, what the current breakthrough may suggest, and then what you as a mother and grandmother and I as a mother might do about it.

As you are very well aware, 180,000 women in America will develop breast cancer this year. Forty-four thousand women in America will die of breast cancer this year. In the 20 years or so I have been working on this disease and the time you have been in the House, 1 million women have died of breast cancer. Everything that I have done in my career in this field has been devoted to the hope that we will be able to preclude the next million deaths over the next 20 years.

About 20 years ago, when I was a post doctoral fellow at the University of California in San Francisco, I decided that I would try to focus on unusual families in which breast cancer appeared to be so common that it was plausible to think that perhaps susceptibility to the disease was being passed from parents to children, that susceptibility possibly being inherited either through the mother or the father's line, although, of course, only women were developing the disease.

This was an unusual tack to take because such families account for, oh, 5, 10 percent of breast cancer at most. Cancer is always ge-

netic, of course, in the sense that cancer always involves changes in the DNA, but usually in the vast majority of cases all of those changes are purely at the level of the target tissue, purely in the breast, purely in the ovary, purely in the prostate and so on, and don't involve inherited alterations. But in these unusual families, it seemed plausible to suspect that perhaps some mutations were being inherited.

Well, it took 17 years to demonstrate that point to a reasonable degree of proof, and in 1990 my group was able to demonstrate that there was a gene on human chromosome 17 that does, indeed, predispose women in these very unusual families to breast and to ovarian cancer.

That set off what became known on the street as the race for the gene, and just this last week, friends and competitors of mine at the National Institute for Environmental Health Sciences, a branch of NIH in North Carolina, at the University of Utah and at Myriad Genetics announced that they had identified the gene itself, that they had actually cloned the gene, that this Friday we will all learn what the sequence of their gene is and we will be in a position to confirm their work. I have every anticipation that we will confirm their work, and this gene that we have all been hunting for for four years and I have been hunting for for 20 will have been found.

Mrs. LLOYD. I just must say that I still give you the credit, so it is all right with me.

Dr. KING. Tell it to my mom. That is the fantasy, the race for the gene and the finding of the gene and The New York Times and glamour girl and all the rest of it.

The reality is that we still don't have a cure. We are all, in genetics, acutely aware of that wonderful speech from Winston Churchill at the end of the Battle of Britain in which he said this is not the beginning of the end. This, however, may be the end of the beginning, and that what we need to do now is use this new information to move forward.

What can we do with this information? I think there are three kinds of things we can do. First, we can develop a very early diagnostic tool for breast cancer. How? The rationale here is that this gene which has inherited mutations in families may also be a gene that is critical to breast cancer development and ovarian cancer development in all of us, in all women who are at high risk of this disease, and indeed we are all at high risk of this disease.

If we can identify those changes specific to the breast and ovary very early on in their development, before they can be identified even by the best mammogram, then we can treat breast cancer in the same way that cervical cancer can now be treated; that is, before it becomes an invasive disease. One can remove the malignant cells with a minimally invasive procedure. The woman goes on with her life. The threat of breast cancer is no longer a death threat.

Second, we can use this information to target malignant cells for women who have escaped the kind of early diagnosis that we hope to be able to put into place in the long run, and if we can target cells better, we can use pharmacologic agents more effectively.

Now, of course, chemotherapy consists of trying to kill the cancer before you kill the patient. It would be enormously beneficial to be able to target the chemotherapy specifically to the kinds of lesions

that are involved and the specific cells that are involved. Molecular genetic information gives us the capacity to do that.

And third, I would like to develop a cure. I would—in genetics terms what that means is we want to reverse the effect of what this gene has done.

Now, one might, in a comic book world, call that genetic engineering. It is in the sense that in the human genome project, what genetic engineering includes is the ability to use genetic information and to introduce a normal sequence, and consequently, the ability to make a normal gene product into the breast cells, into the ovarian cells where formerly that product was no longer being made properly because of the beginning of the tumor.

It is very difficult to do that. I don't have a clue yet. We don't even know what this gene does. I don't have a clue yet how we are going to do it in terms of the specific biology of this gene. However, the tools that we are developing in the human genome project are going to give us the capacity to do it.

So what we have done so far is link the human genome project's tools for identifying the existence of genes in families, cloning the genes in the families, to the biology of this disease. What we now need to do is to link the just now being developed tools of gene therapy in the human genome project to the biology of this disease. That is the marriage of the next 20 years.

Now, what about you and what about me? My half sister had breast cancer at the same age that you had breast cancer yourself. What should we be recommending to our daughters, to your granddaughters? The demand for knowing whether a woman carries a mutation in this first breast cancer gene that has been identified is, I think, going to be enormous.

There are probably over half a million women in America who will develop breast cancer at some time in their lives, or have already, because they have inherited susceptibility to this disease. Now, while that is a very small fraction of all the breast cancer that there is, that is still a very large number of women, and of course, since the presence of the gene may be hidden if it comes in from the father's side and if the family is small, even a family in which there is no apparent family history of the disease may be one in which inherited mutations appear. So what is to be done?

My own sense right now is that we don't know nearly enough yet about this gene for this information to be useful. If I take a sample of your blood now and test for the presence of mutations in this sequence, and I will on Friday be able to do that, either one of two things will happen.

Either I won't find a mutation, or I will find a mutation. If I do not find a mutation in your DNA sequence at this particular genetic locus, it doesn't necessarily mean that you don't have a mutation. It just means that my capacity to find it is not perfect and it is going to be quite awhile, probably a couple of years, before we get to the point that we feel reasonably certain that we are able to pick up all the mutations that there are. But it is still only reasonably certain.

On the other hand, suppose I do find a mutation. What does that mean? We don't know. What we know is that for a small number, maybe a few hundred very high-risk families, which groups, albeit

competitive, but at this point collective, experience indicates have an indeed extremely high risk of breast cancer, we know that among young women in those families, the risk of breast cancer is extremely high. Do we know that your daughter's risk is comparably high? No, we don't know, even if we find a mutation in your sequence. We need to do a good more genetics and epidemiology before we know what risk is associated with what mutations.

Suppose that we even have virtual complete certainty that we—that you do not have a mutation in this gene. There is BRCA2. What about that gene? It is not identified yet. We know it exists, but we don't have it in hand. We know that there are other genes for predisposition to breast cancer, so my plea to young women now is, give the science a little time. Join the hunt. Join the search. Don't make any decisions now that are irremediable because this field is not going to be static. This field is going to move very fast, and over the next years, we hope to be able to offer interventions to women that are far more acceptable and far less drastic than the current interventions that are available.

Thanks.

Mrs. LLOYD. Thank you so very much for your excellent testimony.

Dr. Holtzman, we look forward to hearing from you also.

Dr. HOLTZMAN. Thank you, Mrs. Lloyd, and thank you for giving me the opportunity to discuss some of the implications for society of technological breakthroughs in human genome research.

First, I would like to add my tribute to yours and to that of many scientists to Mary-Claire King for really pointing the way to solving a very difficult problem that many other scientists refused to tackle, the notion that one could look for this—that there was such a gene and one could look for it was really considered much too risky for others to undertake. So she may not have been at the finish line first, but nobody would have gotten there had it not been for her.

Mrs. LLOYD. Thank you for your comments.

Dr. HOLTZMAN. My remarks will focus on new genetic tests made possible by the identification of genes that play a role in human diseases and, at the beginning of her testimony, Professor King made a distinction between the role of genetics in virtually every type of cancer and those very few in which a particular, and I will use this term again, allele of a gene was inherited and increased the predisposition, the susceptibility to cancer, and that operates in a number of other complex diseases, and I am going to limit my testimony to those inherited disorders, the use of genetic tests in those inherited disorders.

By way of background, I am a pediatrician and geneticist, Professor of Pediatrics, Health Policy, and Epidemiology at The Johns Hopkins Medical Institutions. I am a member of the Joint Working Group on ELSI, as you have heard that defined, of both the NIH and the Department of Energy. I am also a recipient of grants from the ELSI program at NIH and much of my research has been at the interface of basic science and medical practice, attempting to understand the role of genes in disease and how breakthroughs in genetics reach the public in the form of tests for genetic disorders.

The discovery of a disease-related gene depends on finding variant forms of the gene, alleles, in people with the disease that are absent in people without the disease. Using recombinant DNA technology, this approach has yielded genes for cystic fibrosis, Huntington disease, muscular dystrophy, neurofibromatosis, Fragile X, familial forms of colon cancer, melanoma, and, as you just heard, breast cancer, to name just a few.

Once these disease alleles are identified, it is technically trivial to devise probes that can be used in clinical settings for detecting healthy individuals who are going to get the disease. Whether the tests can attain this goal safely and effectively is not, however, a trivial matter.

Let me explain why. The initial discovery of a disease-related gene is made in a few families, and that certainly is the way it was for breast cancer. But will the alleles that are associated with disease in these families be the same ones as in others with the disease? Let me give two examples that illustrate the problems.

First, cystic fibrosis. The alleles that proved the identity of the cystic fibrosis gene accounted for fewer than half of all patients with CF. To have begun clinical testing with just these probes would have missed over half the cases. Today we can detect, among white populations, about 90 percent of carriers of cystic fibrosis alleles, but there are still other questions that have to be answered before a recommendation for proceeding with routine screening is made.

The second example is breast cancer, and I could have used colon cancer just as well. Current estimates for both of these cancers is that only about 10 percent of people who will get them have alleles that greatly increase their risk, and the three or perhaps four alleles that have been discovered so far that will be reported in Science Magazine at the end of this week are certainly not the only ones, as Professor King has said.

People who test negative may assume erroneously that their risk is low and fail to take other steps to detect disease early. Negative genetic test results could lull them and their physicians into neglecting the disease as a possible cause when symptoms do appear.

A person from a high-risk family with a negative test result has an appreciably lower risk than before testing and could be spared interventions recommended for those who test positive. This is one important benefit to women in high-risk families, but as Professor King has said, there are still many unanswered questions and the use of such a test in those families should still be viewed investigationaly.

The chance of missing people who carry alleles for disease, what scientists call sensitivity of a test, is not the only error intrinsic to genetic tests. People with positive test results will not always develop the disease or have a high risk of having children with the disease. Scientists call this the predictive value of a positive test.

In high-risk families in which several relatives have colon or breast cancer, people found by testing to have a susceptibility-conferring allele will not always get the disease even if they live past 80.

Cancer is a complex disease in which certain alleles increase susceptibility, but other genetic as well as dietary and environmental factors must be present before malignant lesions appear.

Our understanding of these factors is rudimentary. A woman who is told she has an allele for breast cancer may decide to have a prophylactic mastectomy, but she may never develop breast cancer. The role of genes in other common disorders such as coronary artery disease and mental illnesses is also exceedingly complex.

For single gene, what we call Mendelian genetic diseases, a positive result for being a carrier of a recessive or X-linked disorder seldom carries any risk to the individual. For recessive disorders, the chance that a carrier will have children with a disorder depends on his or her partner also being a carrier. People are not always told and may not understand that a positive test result does not mean that disease will occur in them or in their children. Deficiencies in communication and/or understanding have been documented in carrier screening for sickle cell anemia, Tay Sachs disease, and cystic fibrosis.

Even when positive test results carry a high probability that disease will appear, individuals may not necessarily benefit from the knowledge. First of all, there may be little of proven efficacy that can be done. Fran Visco, the President of the National Breast Cancer Coalition, a consumer organization, pointed out last month that a positive genetic test for familial breast cancer gives a woman information about her risk of getting a disease for which there is no known cure and which she cannot prevent. There are important clues and encouraging findings, but still that is the fact.

Second, people with positive test results risk losing their health insurance as long as insurers can deny coverage or charge higher premiums to those with preexisting conditions, of which inheriting a disease allele is one.

Visco goes on to say that a genetic test for breast cancer may actually do harm because women who test positive risk losing their health and life insurance. Third, genetic tests which are not explicitly included under the Americans with Disabilities Act could be used to deny jobs, even when a positive test result does not impair the worker's ability to perform the job. Employers are also able to exclude conditions for which employees have positive genetic test results from their health benefits.

Fourth, genetic test results could be communicated to relatives or others without the knowledge and permission of the person being tested who might be harmed as a result.

After a disease gene has been identified, much needs to be done, therefore, before that discovery can be translated into effective genetic testing whose benefits outweigh the risks. Despite lack of data on test sensitivity and predictive value, on adverse reactions to testing, or on the efficacy of follow-up interventions, medical centers and commercial clinical laboratories are offering tests for colon and breast cancer and Alzheimer's disease, to name the more common disorders.

They can do this because the Food and Drug Administration, which could require the collection of such data if the test or its components were being sold to other users, has little authority to regulate laboratories who provide these tests as services. The FDA

could, however, require these laboratories to participate in protocols to assess the essential components of genetic testing, most of which have not been approved for clinical use. Unfortunately, the agency does not have the resources to do this.

Nor is there much assurance in most States that the laboratories offering these genetic tests are sufficiently proficient. People are sometimes given wrong information because of avoidable mistakes in the laboratory. Although the Clinical Laboratories Improvement Amendments of 1988 provides a framework for assuring the quality of laboratories performing genetic tests, the Health Care Financing Administration, which administers the Act, has not yet applied its provisions to the specialty of genetic testing.

The decision of a person to have a genetic test is not an easy one. With doubts about the efficacy of interventions to prevent cancer or Alzheimer's disease, for instance, some people would prefer not to know that they are susceptible. Some might fear losing their health insurance if they tested positive.

Carrier testing and prenatal genetic diagnosis present people with options for avoiding the conception or the birth of children with serious genetic disorders. But some people will reject all of these options and would, therefore, prefer not to be tested. Geneticists and genetic counselors who have been trained to present the options in a non-directive manner are in short supply. Their numbers are unlikely to increase substantially. Consequently, non-geneticist physicians, especially primary care physicians, will increasingly provide information to patients about genetic testing.

In work supported by the ELSI program of the National Center for Human Genome Research of the NIH, my colleagues and I have shown that primary care physicians have significant gaps in their knowledge of genetics and genetic testing. Many of them believe it is appropriate to recommend a course of action to their patients in deciding to have a prenatal diagnostic test.

With your permission, I would like to enter the published reports of two of our studies into the record.

Mrs. LLOYD. Without objection, it will be made a part of the record.

[The information follows:]

Physicians' Knowledge of Genetics and Genetic Tests

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Purpose. To assess primary care physicians' and psychiatrists' knowledge of genetics and genetic tests and the factors associated with differences in these physicians' knowledge. **Method.** Questionnaires were mailed in 1991 to 1,795 primary care physicians (family physicians, internists, pediatricians, obstetrician-gynecologists) and psychiatrists who had graduated from medical school between 1950 and 1985 (67.6% of the sample had graduated after 1970) and who were members of professional societies. The questions elicited demographic and practice characteristics as well as knowledge of genetics concepts and facts and awareness of the availability of genetic tests. To validate the questionnaire, 360 medical geneticists and genetic counselors received questionnaires. Statistical analysis involved arc-sine function transformation, *t*-tests, analyses of variance, *F*-tests, Tukey's HSD, and stepwise multiple regression. **Results.** A total of 1,140 (64.8%) of the non-geneticist physicians responded. They correctly answered an average of 73.9%, SD, 13.9%, of the knowledge items, compared with 94.6%, SD, 4.2%,

for the genetics professionals ($p < .001$). The most significant predictors of knowledge were recency of graduation from medical school and practicing in primary care specialties in which exposure to genetics problems is likely. Other significant predictors (from most to least important) were graduation from a U.S. medical school, willingness to adopt a new predictive test before it becomes standard practice, not using pharmaceutical companies as a source of information about new medical practices, and taking a required genetics course in medical school. **Conclusions.** The results suggest that knowledge of genetics and genetic tests is increasing among physicians, particularly among more recent graduates and physicians who are exposed to genetics problems in their practices, but deficiencies remain. Although a medical school course in genetics may improve knowledge, it is not sufficient. Greater emphasis is needed at all levels of medical education to reduce the chance of physician error as more genetic tests become available. *Acad. Med.* 68 (1993):625-632.

As the human genome is mapped, tests to predict the risks of many genetic and gene-influenced diseases will proliferate. Without a marked expansion in the training of medical geneticists and master's-level genetics counselors, which seems unlikely,^{1,2} primary care physicians will increasingly offer genetic tests to their patients.³ Adequate knowledge of genetics and genetic tests, including the ability to interpret probabilistic information, is a prerequisite to their ability to do so.

Little is known about physicians' knowledge of genetics⁴⁻⁷ or their awareness of the availability of tests for genetic disorders.^{8,9} Three of the available studies were conducted in the United States,^{4,6,7} and all but one⁸

were performed before 1981. All of them were limited to specific groups of primary care providers and did not compare these providers' knowledge with that of medical geneticists.

The principal objective of this study was to assess primary care physicians' and psychiatrists' knowledge of medical genetics and the availability of genetic tests. The questions were developed to elicit knowledge that geneticists and a panel of primary care providers considered to be important for evaluating and counseling in a primary care setting and that did not require advanced training in genetics. Psychiatrists were included because of the increasing interest in the role of genes in psychiatric disorders. We also determined the extents to which demographic, educational, and practice characteristics were associated with respondents' knowledge.

METHOD

Sample

A detailed description of the survey method appears elsewhere.⁸ Primary care physicians (family physicians, internists, obstetrician-gynecologists, pediatricians) and psychiatrists were selected in 1991 from

the American Medical Association (AMA) Physician Masterfile. Physicians in each specialty were sampled in equal numbers from the following states: California (Los Angeles County only), Illinois, Maine, Nebraska, New York (upstate only), Oregon, Pennsylvania, South Carolina, Texas, and Utah. (One state was selected at random from each of the ten Genetics Network Regions established by the Health Resources Administration, U.S. Department of Health and Human Services.) In each state, physicians within each specialty who had graduated from medical school between 1971 and 1985 were sampled in a ratio of two to one compared with those who had graduated between 1950 and 1970. Participation was invited only from members or candidate members of the following societies (as determined by a search of the societies' directories): American Academy of Family Physicians (AAFP), American College of Physicians (ACP), American College of Obstetricians and Gynecologists (ACOG), American Academy of Pediatrics (AAP), and American Psychiatric Association (APA). The members of these societies are predominantly board-certified.

The final sample included 1,795 physicians: 358 family physicians,

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360 internists, 360 obstetrician-gynecologists, 359 pediatricians, and 358 psychiatrists. To validate the survey instrument, 180 medical geneticists and 180 genetic counselors in the same ten states were sampled from membership lists provided by the American Board of Medical Genetics (ABMG).

Survey Instrument

Facts and concepts questions were developed by geneticists and genetic counselors at The Johns Hopkins Medical Institutions and modified after input from eight primary care physicians (two from each specialty) and two psychiatrists. Further refinements were made after a pretest on a national sample of physicians.⁹ Except for some questions about respondents' demographic characteristics, a multiple-choice, yes-no, or matching format was used. The questionnaire took approximately 30 minutes to complete.

The knowledge portion of the questionnaire consisted of two components: 17 concepts questions, of which six required pedigree interpretation, six probed the understanding of terms, and five determined familiarity with the use of probability in medical genetics (of which four required some computation); nine facts questions, of which three dealt with characteristics of genetic disorders and six with the availability of deoxyribonucleic acid (DNA) or biochemical tests for specific diseases.

A latent-imaging technique was used for a section of the questionnaire dealing with cystic fibrosis. Using a special pen, respondents could reveal additional narrative after answering certain questions. This allowed them to base subsequent answers on accurate information provided in the narrative.

Procedures

The questionnaire was mailed to the entire sample. In an effort to increase the response rate, we offered the non-geneticist physicians (i.e., the primary care physicians and psychiatrists) \$25 for completing the survey. In addition, continuing medical edu-

cation (CME) credits were offered for completing the questionnaire and studying additional material. Endorsements were obtained from the relevant medical specialty societies and from local chapter heads of three of the societies. Follow-up included postcard reminders, questionnaire remailings, and phone calls from a survey research firm with which we contracted.⁹ As no difficulty was anticipated in obtaining an adequate response from the medical geneticists and genetic counselors, incentives were not offered to these participants.

Analysis

An overall knowledge score was created by assigning one point for each correct answer (the one four-part question was assigned one-fourth of a point for each correct answer), for a possible total score of 26; 17 for concepts and 9 for facts. We considered a 10% difference in correct responses to a component score to be a meaningful difference and selected our sample sizes accordingly. To adjust for skewness, the knowledge scores were transformed by the arc-sine function. Taking the means of the arc-sine-transformed values, we used *t*-tests to compare the total and component knowledge scores of the genetics specialists with those of the non-geneticist physicians. Analyses of variance (ANOVAs) were performed to compare the transformed knowledge scores of the different primary care specialists and psychiatrists. When the overall *F*-test was significant, Tukey's HSD was used to determine significance for the pairwise differences. The significance level was set at $p < .05$. Two-way ANOVA was used to examine joint effects of selected variables. Stepwise multiple regression was used to adjust for covariance among variables associated with knowledge scores.

RESULTS

Response Rate and Demographic Characteristics

The response rate from the non-geneticist physicians was 64.8% (1,140 physicians): family physi-

cians, 62.0% (215); internists, 61.0% (214); obstetrician-gynecologists, 62.9% (224); pediatricians, 72.6% (257); and psychiatrists, 65.5% (230). A significantly higher percentage of the respondents than the nonrespondents were graduates of U.S. medical schools (86.7% versus 77.2%).⁹ The response rate from the medical geneticists and genetic counselors was 79.1% (280). As expected, given our design, approximately two-thirds of the non-geneticist physicians (771, 67.6%) had graduated from medical school between 1971 and 1985. Of all the non-geneticist physicians who responded, 15.0% held full-time faculty positions, 25.9% held part-time positions, 12.4% had other academic positions, and 46.7% had no academic position. Of the family physicians who responded, 28.9% were family physicians who delivered babies (FPDs), 69.3% were family physicians who did not deliver babies (FPNDs), and 1.9% did not indicate whether they delivered babies or not. Not all respondents answered every question.

Genetics Knowledge

Total scores. The mean total knowledge score of all the non-geneticist physicians was 73.9% correct, compared with 94.6% for genetics professionals ($p < .001$), as shown in Table 1. The distribution of the total scores is shown in Figure 1.

Individual knowledge questions. The non-geneticist physicians who were most likely to encounter patients with specific genetic problems had the greatest knowledge regarding those problems: the pediatricians knew the most about the features of cystic fibrosis (CF); the obstetrician-gynecologists and FPDs were best able to provide the correct information regarding the detection of birth defects (96% and 80.6% correct, respectively); the psychiatrists scored highest on the question relating to the heritability of depression (96.1% correct). After being told the frequency of cystic fibrosis carriers, 473 (41.6%) of the physicians correctly calculated the chance that a couple with a family history that is negative for cystic fibrosis could have a child with a dis-

order. Almost one-third (354, 31.2%) could not determine the mode of inheritance from a pedigree, and 314 (27.6%) were unaware of long-established tests for sickle-cell anemia.

Academic status. The non-geneticist physicians who were full-time faculty had a total knowledge score significantly higher than that of the other non-geneticist physicians (Table 1), but significantly lower than that of the medical geneticists.

Factors Influencing Knowledge Scores

The analyses described in this section are based on responses from the 966 non-geneticist physicians who were not full-time faculty. With few exceptions, the differences observed between groups of non-full-time faculty respondents were also observed between the comparable groups of full-time faculty; the scores of the full-time faculty were significantly higher than those of the comparable non-full-time faculty in most cases. The mean knowledge score of the non-geneticist physicians who were full-time faculty was not associated with having taken a required medical school course in genetics.

Clinical specialty. The mean total knowledge score as well as the two mean component scores differed significantly by specialty. The pediatricians scored significantly higher than all the other groups of physicians on total knowledge and concepts. On the facts component, the obstetrician-gynecologists (74.4% correct) and the pediatricians (72.2% correct) scored significantly higher than did the internists (63.3% correct), psychiatrists (58.9% correct), and FPDs (64.4% correct). The FPDs (72.2% correct) also scored significantly higher than did the psychiatrists. On the total score, 41.0% of the FPDs, 40.3% of the psychiatrists, and 33.1% of the internists had scores of less than 66% correct compared with 13.4% of the pediatricians, 23.5% of the obstetrician-gynecologists and 21.4% of the FPDs (chi-square = 53.9, $p < .00001$).

The pediatricians, obstetrician-gynecologists, and FPDs were exposed to genetics problems in their

Table 1
Mean Scores of Total Genetics Knowledge for 280 Genetics Professionals Compared with the Scores for 1,140 Primary Care Physicians and Psychiatrists, 1991*

Survey Respondents	Total Genetics Knowledge		
	Numerical Score		Mean % Correct
	Mean	(SD)	
Genetics professionals (<i>n</i> = 280)	24.6	(1.1)†	94.6
Medical geneticists (<i>n</i> = 141)	24.6	(1.2)	94.6
Genetics counselors (<i>n</i> = 139)	24.7	(1.0)	95.0
Primary care physicians and psychiatrists (<i>n</i> = 1,140)	19.2	(3.6)†	73.9
Full-time faculty (<i>n</i> = 171)	20.2	(3.3)‡	77.7
Other non-geneticists (<i>n</i> = 966)	19.0	(3.6)‡	73.1

*The primary care physicians (family physicians, internists, pediatricians, obstetrician-gynecologists) and psychiatrists had graduated from medical school between 1950 and 1985 (67.6% after 1970) and were all members of professional societies. They completed a 26-item questionnaire testing their knowledge of genetics, with a maximum score of 26.

†For genetics professionals versus primary care physicians and psychiatrists: $t = 43.8$, $p < .001$.
‡For primary care physicians and psychiatrists who were full-time faculty versus those who were not: $t = 4.18$, $p < .001$.

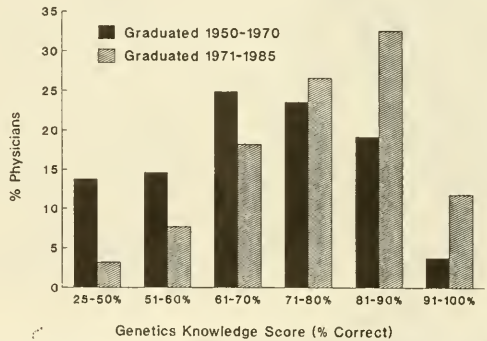


Figure 1. Distribution of scores for total genetics knowledge of 369 non-geneticist physicians who had graduated from medical school between 1950 and 1970 and 771 who had graduated between 1971 and 1985. The physicians were primary care physicians (family physicians, internists, pediatricians, obstetrician-gynecologists) and psychiatrists. In 1991 they completed a 26-item questionnaire testing their genetics knowledge. Limiting the analysis to the 966 physicians who were not full-time faculty does not appreciably change the distributions.

Table 2

Multiple Regression Analyses of Predictors of Genetics Knowledge Scores for 969 Primary Care Physicians and Psychiatrists, 1991*

Genetics Knowledge Score	Predictor B	R ² change	Significance of F change (p)	Total R ²
For total knowledge				
Year of medical school graduation	.006	.113	<.0001	.113
High versus low exposure to genetics in practice	.111	.075	<.0001	.188
U.S. versus foreign medical school	.093	.028	<.0001	.216
Innovativeness†	.023	.013	<.0001	.229
Drug company as source of information	-.046	.010	<.001	.240
Required medical school course in genetics	.039	.007	<.01	.247
Joint effect of medical school course and postgraduate exposure	.031	.005	<.05	.252
For concepts				
Year of medical school graduation	.009	.124	<.0001	.124
High versus low exposure to genetics in practice	.094	.033	<.0001	.157
U.S. versus foreign medical school	.105	.023	<.0001	.180
Innovativeness†	.028	.013	<.0001	.193
Drug company as source of information	-.049	.009	<.01	.202
Required medical school course in genetics	.035	.004	<.05	.206
For facts				
High versus low exposure to genetics in practice	.163	.075	<.0001	.075
Year of medical school graduation	.004	.019	<.0001	.093
U.S. versus foreign medical school	.097	.012	<.001	.105
Required medical school course in genetics	.053	.007	<.01	.112

*The primary care physicians (family physicians, internists, pediatricians, obstetrician-gynecologists) and psychiatrists had graduated from medical school between 1950 and 1985 (67.6% after 1970), were all members of professional societies, and were not full-time faculty. They completed a questionnaire with 26 questions testing their total knowledge of genetics, 17 testing knowledge of genetics concepts, and nine testing knowledge of genetics facts.

†Innovativeness: the likelihood that physicians would offer a genetic test before it became standard practice.

practices more frequently than were the FPNs, internists, and psychiatrists. For instance, 81.6% of the former indicated they provided genetic counseling, compared with 52.9% of the latter (chi-square = 91.3, $p < .00001$). To simplify exploration of the effect of exposure to genetics in clinical practice, we created a dichotomous variable, *exposure to genetics in practice*. The 543 respondents who were pediatricians, obstetrician-gynecologists, or FPDs were defined as *high-exposure physicians*, and the 593 respondents who were FPNs, internists, or psychiatrists were defined as *low-exposure physicians*. The high-exposure physicians had a mean knowledge score (77.3% correct) that was significantly higher ($p < .001$) than that of the low-exposure physicians (69.2% correct).

In three separate multivariate re-

gression analyses, with total knowledge, concepts, and facts scores as the dependent variables (Table 2), exposure to genetics in practice provided the second-most significant explanation for the variance in total knowledge and concepts scores, and the most significant for the facts score. Its smaller effect on the concepts score was due to the disparity between the scores of the pediatricians (84.1% correct) and those of the obstetrician-gynecologists and FPDs (75.9% correct and 74.1% correct, respectively).

Year of graduation from medical school. As Figure 2 shows, for both the high- and low-exposure physicians there was a significant upward trend in mean total knowledge scores as a function of year of graduation from medical school. The physicians who had graduated after 1970 had a higher mean knowledge score (76.2% cor-

rect) than those graduating earlier (66.9% correct, $p < .001$; distribution of scores shown in Figure 1). As shown in Table 2, in multivariate analysis, year of graduation from medical school was the most powerful predictor of the total and concepts scores and the second-most powerful predictor of the facts score.

Formal course work in genetics. The effect of year of graduation could be due to the upward trend in the percentages of the physicians who had had a genetics course in college or a required course in genetics in medical school (Figure 3). The physicians who reported having had a required course in medical school had a significantly higher mean knowledge score (75.4% correct) than did the physicians who reported having had no course in genetics (70.4% correct, $p < .001$). We found no significant difference in mean knowledge scores between the

physicians who had had a required genetics course in medical school and those who had had a college course instead of or in addition to a medical school course. Having a required medical school course in genetics was a significant predictor of total, concepts, and facts scores, but accounted for no more than 0.7% of the variance (Table 2). Year of graduation was a more potent predictor in the multivariate analysis.

Having taken a required medical school course in genetics was associated with greater knowledge for the physicians in high-exposure specialties than for those in low-exposure specialties (two-way ANOVA interaction, $F = 6.7$, $p = .01$). The joint effect of having a medical course and of high exposure to genetics in practice was also significant in the multivariate model for total knowledge score (Table 2).

Country of medical school. Graduation from a U.S. medical school was a significant predictor of knowledge in univariate and multivariate analysis (Table 2). The physicians who had graduated from U.S. medical schools had a higher mean knowledge score (74.2% correct) than did those who had graduated from foreign medical schools (66.9% correct, $p < .001$). This could not be attributed to a higher proportion of U.S. graduates having taken a required medical school genetics course, as virtually equal percentages of U.S. and foreign medical graduates (55.1% versus 54.1%) had taken such a course. The respondents who were foreign medical graduates were no more likely to have entered specialties with low exposure to genetics than were the graduates of U.S. schools.

Information sources. We asked the physicians to indicate their most frequent sources of information about new medical practices. They could choose more than one. The most frequent sources, in descending order, were medical journals, CME courses, other practitioners, professional meetings, and pharmaceutical contacts. The 413 physicians who reported a pharmaceutical company contact as a frequent source of information had a significantly lower

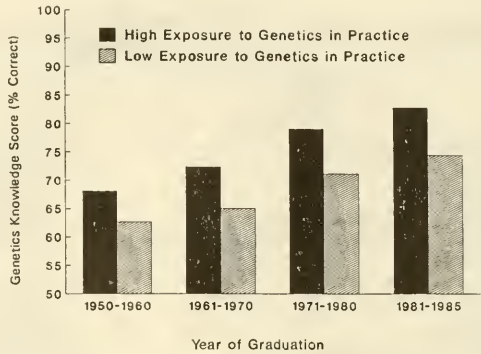


Figure 2. Mean scores (% correct) for total genetics knowledge by year of graduation from medical school for 543 physicians with high exposure to genetics in their practices and 593 physicians with low exposure. The high-exposure physicians were pediatricians, obstetrician-gynecologists, and family physicians who delivered babies, and the low-exposure physicians were internists, psychiatrists, and family physicians who did not deliver babies. In 1991 the physicians completed a 26-item questionnaire testing their genetics knowledge. Excluded from this analysis were 171 physicians studied who were full-time faculty.

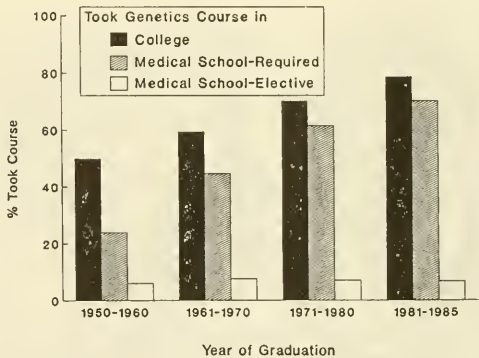


Figure 3. Percentages of 966 non-geneticist physicians by year of graduation from medical school who had taken at least one course in genetics. The physicians, who were surveyed in 1991, were primary care physicians (family physicians, internists, pediatricians, and obstetrician-gynecologists) and psychiatrists. Excluded from this analysis were 171 physicians studied who were full-time faculty.

mean knowledge score (71.2% correct) than did the physicians who did not use pharmaceutical contacts as a frequent information source (74.6% correct, $p < .001$). Using such contacts was a significant negative predictor in the multivariate analyses for total and concepts scores (Table 2). The 474 physicians practicing in groups reported other practitioners as a frequent source (83.3%) more often than did the 329 solo practitioners (72.3%, chi-square = 13.9, $p = .0002$). The family physicians reported that drug company representatives were a frequent source of information to a significantly greater extent than did the other physicians (43.2% versus 28.7%; chi-square = 14.8, $p = .00012$). The mean total knowledge scores did not differ between the 88% of the physicians who reported CME courses as frequent sources and the remaining 12%.

Innovativeness. Physicians who adopt a new technology when it first becomes available may have a greater fund of knowledge than those who are slower to adopt such technology. We attempted to identify early adopters by asking the respondents to rank (on a six-point scale from 1, very unlikely to 6, very likely) how likely it was that they would routinely offer a hypothetical test to their patients. The test identifies people who "will manifest a common disease in the future" and is "low cost" and "accurate." An intervention for people with positive test results "can improve their prognosis." Fifty-one percent of all the non-full-time faculty physicians said they would be likely to offer it when no others in their specialty did (25% ranked 6; 26% ranked 5). A total of 74% said they would be likely to offer it (rank of 5 or 6) when others were using it but before it became "standard practice"; 97% said they would be likely to offer it when it became standard practice. The internists were more likely than all the other specialists combined to offer the test when it first became available (chi-square = 12.0, $p = .003$). The early-adopting physicians, i.e., those who would be likely to offer the test before it became standard practice, had a

significantly higher mean knowledge score (74.2% correct) than did those who would be likely to adopt it only after it was standard practice (70% correct, $p < .001$). The early-adopting physicians in the high-exposure specialties had a significantly higher mean knowledge score than did the early adopters in the low-exposure specialties (20.3, SD, 3.2 versus 18.3 SD, 3.6; $t = 7.8$, $p < .001$). There was no interaction between specialty and early adoption. Being an early adopter, or innovative, was a predictor of total and concepts knowledge scores in the multivariate regression analyses (Table 2).

Other factors. The physicians practicing in groups had a higher mean knowledge score (75% correct) than did the solo practitioners (71.2% correct, $p < .001$). The physicians who indicated that they or an immediate family member had received genetic counseling had a significantly higher mean knowledge score (76.2% correct) than did those who responded that they had not (72.3% correct, $p < .01$). The mean knowledge score of the 90 rural physicians did not differ from that of the physicians practicing in urban or suburban areas. None of the three factors discussed in this paragraph was a significant predictor in multivariate analysis.

DISCUSSION

The mean knowledge score of the genetics professionals (94.6%, SD, 4.2%) validates our knowledge questions. It also serves for comparison with the scores of the non-geneticist physicians. Although these physicians' average score was 78%, their errors reflect deficiencies deemed important by the non-geneticist physicians who helped us design the survey. Moreover, the distribution of scores is broad, with over half of the non-geneticist physicians who had graduated from medical school before 1971 having scores of 70% or less (Figure 1). Particularly noteworthy were frequent errors in problems involving probabilities, a deficiency

that has been observed before.¹⁰ Although we obtained higher response rates than previous studies,⁴⁻⁷ the failure of 35% of the non-geneticist physicians to respond limits generalizability.

Our sample was intentionally biased toward the overrepresentation of physicians who were more likely to attain higher scores. We limited our sample to members of professional societies and over-sampled more recent graduates. The upward bias of the scores also resulted from the characteristics of the respondents. A higher proportion of nonrespondents than respondents had graduated from non-U.S. medical schools,⁹ a factor associated with lower knowledge scores. (The higher knowledge scores of the U.S. medical school graduates than of the graduates of foreign schools has been observed in other knowledge areas as well.¹¹) The upward bias of the scores could also have resulted if the respondents had looked up answers or uncovered the latent-image messages before answering certain questions (despite instructions to the contrary). As a deterrent to such practices, the physicians were assured that responses would be analyzed without identifiers, which they were.

By limiting our analyses of factors associated with knowledge scores to the respondents who were not full-time faculty members, we introduced a downward bias in knowledge scores. We did this because we were primarily interested in practitioners rather than current teachers and investigators. Full-time faculty status was a predictor of higher knowledge scores in a multivariate analysis (not shown) that included all of the variables shown in Table 2. Full-time faculty are more likely to have patients for whom genetic diseases have to be considered in the differential diagnosis. These physicians may be exposed to genetics through interactions with medical geneticists on their faculties more often than physicians with part-time or no academic affiliation. The knowledge gained from such contacts may explain why having a required genetics course in medical

school had no significant impact on full-time faculty members' knowledge of genetics. Significantly more of the full-time faculty than the non-full-time faculty reported "other practitioners" as a frequent source of information about new medical practices (87.1% versus 78.8%; chi-square = 6.7, $p = .01$).

This study was undertaken to gain an indication of the preparedness of non-geneticist physicians to deal with the expected increase of genetic tests that they will have to offer. The results are encouraging in that more recent U.S. medical school graduates and those in specialties that have greater exposure to genetics had higher scores (Table 2). The question of what can be done to improve knowledge further remains. This is especially daunting in the case of physicians in specialties in which predictive genetic tests are not currently important but will be. Likely candidates among predictive tests include presymptomatic tests for adult polycystic kidney disease, hemochromatosis, breast cancer, colon cancer, coronary artery disease, Alzheimer's disease and, perhaps, some psychoses and affective disorders, as well as tests for single gene disorders such as cystic fibrosis and Duchenne's muscular dystrophy in healthy adult carriers. Practitioners in low-exposure specialties have not yet begun to narrow the gap between their knowledge of genetics and that of physicians in high-exposure specialties (Figure 2).

For physicians in both low- and high-exposure specialties, increasing coverage of genetics in medical school will be important. The most likely explanation for the higher scores of the more recent graduates is the increasing attention being given to genetics in medical school curricula. The salutary effect of recent graduation, however, is not limited to genetics¹¹ and could be due to more recent graduates' reading and/or retaining more information. Nor does having a required course in genetics account for most of the greater knowledge of more recent graduates. The increasing attention paid to genetics elsewhere in the curriculum could

be responsible. Nevertheless, the synergistic effect on the total knowledge score of having had a genetics course in medical school and of being a physician in a high-exposure specialty suggests a beneficial effect of such courses. Evidence for a direct effect of a genetics course on knowledge comes from a study in which time devoted to teaching genetics to medical students was a predictor of the students' abilities to correctly answer genetics questions on the National Board of Medical Examiners examination.¹²

Beyond medical school, physicians have a number of ways of becoming familiar with new genetic tests. Although we have not documented it, increasing attention is being paid to genetics in both pediatrics and obstetrics residency programs. In obstetrics in particular, technical bulletins prepared by the professional society acquaint physicians with new prenatal tests and their appropriate uses.

A number of other sources of medical information are available to practicing physicians. We included the importance the respondents placed on each of them in our model of factors influencing physicians' knowledge of genetics. The only significant predictor was a negative one. The physicians who reported using pharmaceutical companies had less knowledge of genetics than did those who relied on other sources. This group of physicians may devote less time to alternative sources in which knowledge of the type tested in our survey is imparted. Knowledge was not greater for those who reported CME courses. Relatively, few such courses on genetics have been offered to physicians thus far. There is, moreover, conflicting evidence on the effectiveness of CME courses.¹³⁻¹⁶

No formal survey can indicate the actual ways in which physicians respond to the problems of individual patients. With genetic testing frequently mentioned in the lay press, patients will often initiate questions about testing. Some physicians who are unfamiliar with the tests in question will make it their business to find out before answering. If this happens

frequently, the knowledge score in our survey would be a poor predictor of actual practice. On the other hand, there are instances in which physicians' failure to inform patients of new genetic tests, partly because the physicians were unfamiliar with them, have resulted in successful liability litigation when the patients or their children have suffered harmful consequences from not being tested.¹⁷ It would, of course, be preferable to adopt genetic tests in an appropriate manner before any patient or physician suffers the adverse effects of lack of knowledge. Unfortunately, some educational efforts are driven more by the potential for litigation than by medical practice concerns.¹⁸

Potential users of a new technology do not adopt it all at once. One of the attributes of early adopters is greater knowledge of the technology.^{19,20} Our findings are consistent with this observation. The physicians who indicated they would adopt an efficacious predictive test before it became standard practice had greater genetics knowledge than did later adopters. Nevertheless, the innovators in the low-exposure specialties had, on average, less knowledge about genetics than both the early and late adopters in the high-exposure specialties. After they adopt a new technology, local innovators often play a more important role in its subsequent diffusion than do national consensus statements^{21,22} and, perhaps, formal CME.

Knowledge alone will not determine the adoption of a new technology. Characteristics of the technology itself, as well as the time involved, costs, and mechanisms of payment,^{3,23} are important determinants. The unique implications of genetic tests,²⁴ and the concerns already made public about them, suggest that diffusion should not proceed more rapidly than providers can gain adequate understanding of them. Currently, since many individuals are unaware of the implications of genetic testing, physicians must also be prepared to explain benefits and risks and respond to concerns in order to assure use that is consonant with their patients' personal values.

CONCLUSIONS

We have demonstrated substantial variation in knowledge of genetics and genetic tests among predominantly board-certified physicians in primary care specialties and psychiatry. Deficiencies are likely to be greater among the general population of practicing physicians. It is encouraging, however, that genetics knowledge is greater among recent graduates. Moreover, physicians confronted with a clinical "need to know" seem able to improve their genetics knowledge. How to accelerate the understanding of genetics, particularly in specialties that currently do not accord importance to genetics but may soon need to, is a challenge. Improving the appreciation for the contribution of genetic factors to disease during medical school and residency may necessitate increasing the proportions of genetics questions on certifying examinations, although this may be insufficient. Finally, curriculum planners should ensure that instruction in genetics (including relevant skills such as the interpretation of probabilistic results and the counseling of patients) is integrated throughout all years of medical school and is provided to residents in primary care.

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Incorporation of Genetics in Primary Care Practice

Will Physicians Do the Counseling and Will They Be Directive?

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Objective: To determine, by response to a scenario, how willing primary care physicians would be to counsel a couple about prenatal diagnosis of cystic fibrosis and how directive they would be about whether the couple should undergo prenatal diagnosis and whether the couple should terminate the pregnancy if the fetus is affected.

Design: Survey of a random sample of primary care physicians, psychiatrists, and genetics professionals in 10 geographically representative states.

Respondents: Sixty-five percent (N=1140) of 1759 obstetricians, pediatricians, internists, family practitioners, and psychiatrists, and 79% (N=280) of medical geneticists and genetic counselors.

Outcomes and Results: Respondents were evenly divided on whether they would counsel about prenatal diagnosis or refer to a genetic counselor (49.4% and 50.6%, respectively). Those who indicated that they would counsel were likely to have greater knowledge

about genetics, greater confidence in communicating about genetics, and higher tolerance for ambiguity and were more likely to have completed their medical training since 1971 and to practice in a rural area. Forty-four percent of physicians would give an opinion about prenatal diagnosis. Men would be more likely to give an opinion than women ($P<.005$). Only 9.6% of respondents would give an opinion regarding abortion. These respondents were more likely to come from specialties with less exposure to genetics and to value attendance at religious services. Primary care physicians were more likely to give their opinions about prenatal diagnosis and abortion than genetics professionals.

Conclusions: To the extent that attitudes are reflected in practice, genetic counseling may be more directive when provided by primary care physicians than by genetics professionals, unless primary care physicians' growing involvement in genetics changes their attitudes.

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WITH THE proliferation of new genetic tests that will detect carriers of disease-causing genes and predisposition to disease and will diagnose disease presymptomatically, there will be an insufficient number of trained genetics professionals to offer testing.¹ Consequently, genetic testing is increasingly likely to become a part of primary care practice.^{2,3} To adapt to such rapid advances in genetic information and diagnosis, physicians will have to examine their role in making this information available to their patients at several stages of decision making. The incorporation of genetic testing into clinical medicine is currently in a transitional phase, where the information about the advantages and disad-

vantages of genetic tests is still incomplete and professional norms have not yet evolved to take into account new developments.⁴

Little is known about how primary care physicians will incorporate new genetic technologies into their practices. Some might resist offering their patients genetic services for various reasons: they lack experience and confidence in discussing genetics; they feel burdened and overwhelmed by what seems like an increasing list of obligations in the face of decreasing time and resources; or they

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See Methods on next page

METHODS

STUDY DESIGN AND POPULATION

An equal number of primary care physicians (family physicians, internists, obstetrician-gynecologists [hereafter referred to as obstetricians], and pediatricians) and psychiatrists were selected at random from the American Medical Association Physician Masterfile for each of the following states: New York, Illinois, Nebraska, Pennsylvania, Utah, Maine, Oregon, California, South Carolina, and Texas. (Each of these states was selected at random from the 10 Genetics Network Regions established by the Health Resources Administration—Department of Health and Human Services). Because the overall study was intended to focus on what has recently been taught in medical schools, physicians (the term *physicians* will be used to refer to primary care physicians and psychiatrists) within each specialty who graduated between 1971 and 1985 were sampled at a ratio of 2:1 to those who graduated between 1950 and 1970. Only members or candidate members of the following societies (as determined by a search of their directories) were retained in the sample: American Academy of Family Physicians (AAFP), American College of Physicians (ACP), American College of Obstetricians and Gynecologists (ACOG), American Academy of Pediatrics (AAP), and American Psychiatric Association (APA). They are predominantly board-certified. To validate the survey instrument and for comparison, medical geneticists and genetic counselors were included in the study and sampled from membership lists provided by the American Board of Medical Genetics. A detailed description of survey methods appears elsewhere.⁸

PROCEDURES

A questionnaire was mailed to all eligible physicians with a promise that we would not link names and individual responses. In an effort to maximize our response rate, physicians were offered \$25 and continuing medical education credits for completing the questionnaire. In addition, endorsements were obtained from the relevant medical specialty societies and from local chapter heads of three of the societies. Follow-up included postcard reminders, questionnaire remainings, and phone calls.

have ethical concerns about the value and implications of genetic testing. Among those who might welcome the opportunity to incorporate genetic services into their practices, it is not known whether or to what extent they would be nondirective in interactions with patients. Nondirectiveness certainly has not been as much of a focus of primary care training as it has been of genetics training. Moreover, despite the belief among most genetics professionals that genetic counseling should be nondirective,⁵ the desirability and practicality of nondirectiveness is currently being challenged even in genetics circles.^{6,7}

As part of a larger descriptive survey conducted in 1991

CONSTRUCTION OF VARIABLES

All items in this component of the questionnaire were in multiple-choice format. The instructions for responding to the CF scenario conceded that some of the questions might not be relevant to the respondent's specialty but encouraged all respondents to complete the entire scenario. The scenario presented physicians with the following three hypothetical situations

OUTCOME VARIABLES

1. Referral for Genetic Counseling

Respondents were told to imagine a pregnant couple coming to them, both carriers of the gene for CF. Respondents then were asked whether they would "discuss prenatal diagnosis with the couple before (or instead of) referring them to a genetic counselor" or "immediately refer them to a genetic counselor." This question was not presented in a general way. It was preceded in the scenario by several questions that were very specific to this couple's situation and allowed the respondent to assess his or her own knowledge level about this couple's risk. Therefore, by the time respondents reached this question, they would be quite clear about whether they would feel capable of handling the case themselves or would make a referral. Regardless of whether they said they would discuss or refer, respondents were then told that the couple returned to them to decide about prenatal diagnosis.

2. Opinion Regarding Prenatal Diagnosis

Respondents then were asked whether, in discussing the pros and cons of prenatal diagnosis with this pregnant carrier couple, they would "give their opinion about whether it is a good idea but emphasize that they have to make their own decision" or "refrain from expressing an opinion or giving advice and emphasize that they have to make their own decision" as to whether the woman should undergo prenatal diagnosis.

3. Opinion Regarding Abortion

Respondents then were asked to imagine that this same couple has prenatal diagnosis and that the fetus has CF. Respondents were asked what kind of opinion they would give the

to assess physicians' and genetics professionals' knowledge of genetics and genetic testing, we investigated physicians' perceptions of their role in prenatal genetic counseling, using cystic fibrosis (CF) as a case study. We were interested in how willing physicians would be to discuss prenatal diagnosis of CF with a couple found to be carriers of the CF gene and how directive they would be when discussing whether the couple should undergo prenatal diagnosis and whether they should terminate the pregnancy if the fetus is affected. In addition, we were interested in how physicians' specialty, as well as their knowledge of genetics, confidence in communicating about genetics, tolerance for ambiguity, and

couple about terminating the pregnancy. Choices included (1) "recommend that the mother continue the pregnancy because of (a) moral objection to abortion or (b) the improved outlook for a child with CF born today," (2) "recommend that the mother terminate the pregnancy because of (a) the burden that a child with CF will be to the child and the family or (b) the burden that a child with CF will be to society," and (3) "make no recommendation, review the issues and options with the couple, and indicate that they must decide whether to continue or terminate the pregnancy." Responses were divided into those in which an opinion of any kind would be given vs those in which no opinion would be given. Both opinion variables (regarding prenatal diagnosis and abortion) were taken as measures of directiveness in communication.

PREDICTOR VARIABLES

Specialty

In addition to sampling four primary care specialties, psychiatrists were included because of their potential involvement in genetic testing, eg, for susceptibility to major affective disorders. For comparison purposes, medical geneticists and genetic counselors also were included in the sample. Genetics professionals were instructed to skip the question about "referral."

Knowledge

Knowledge scores were derived from the number of correct responses to 26 knowledge questions. A detailed description of the development and results of the knowledge test appears elsewhere.⁹

Tolerance for Ambiguity

A previously validated seven-item scale was used to measure people's general reaction to ambiguous situations. Respondents were asked to rate the extent to which they agreed or disagreed with each item. Overall tolerance for ambiguity scores were then created by summing the responses. The reliability, based on Cronbach's α test, was .75. A detailed description of the psychometric analyses involved in scale development appears elsewhere.¹⁰

Confidence

A scale of confidence in communicating about genetic testing was developed, modeled after previous work.¹¹⁻¹³ For each of nine items, respondents were asked to check off one of six response categories, ranging from "not at all confident" to "very confident." A total confidence score was created by summing responses to the individual items. The reliability of the scale was .89 (Cronbach's α test).

Attendance at Religious Services

Respondents were asked the extent to which it was important to attend religious services regularly, using a six-point scale ranging from "very unimportant" to "very important." Based on the frequency distribution of responses, a dichotomous variable then was created for subsequent analysis (those who said "very important" vs everyone else).

Year of Graduation

Consistent with the decision we made to oversample recent graduates from medical school, we dichotomized year of graduation into those who graduated from 1971 through 1985 and those who graduated prior to 1971.

Geographic Area

Respondents were grouped into those who reported practicing in a rural area vs elsewhere (urban, suburban, or small city).

ANALYSIS

Knowledge, confidence, and tolerance for ambiguity scores were dichotomized according to the frequency distributions of the respective scores, with the 50th percentile falling in the upper group. Physicians in the higher knowledge group had scores of at least 75% correct. Once all variables were in categorical form, χ^2 tests of association were used to look at the relationship between outcome and predictor variables. Stepwise logistic regression was used to adjust for confounding effects of the several characteristics associated with referring to a genetic counselor and giving opinions about pregnancy termination. All analyses were done using SPSS/PC+.

demographic characteristics, contributed to variations in the likelihood that they would discuss prenatal diagnosis and be directive in their discussions.

RESULTS

RESPONSE RATES

In calculating response rates, questionnaires that did not reach the intended respondent because of death, retirement, or relocation were not included. The response rate from medical geneticists and genetic counselors was 79.1%. The

response rate from physicians was 64.8%, ranging from 61% for obstetricians to 72.6% for pediatricians. Respondents were more likely to be younger than 40 years and to have graduated from medical school after 1977. A detailed analysis of differences between respondents and nonrespondents appears elsewhere.⁸

PHYSICIANS' PERCEPTIONS OF THEIR ROLE IN PRENATAL GENETIC COUNSELING

With respect to the three outcome variables, physicians who responded were evenly divided as to whether they

Table 1. Directiveness of Physicians vs Genetics Professionals in Prenatal Genetic Counseling

Measure of Directiveness	No. Responding (% Responding Yes)		
	Primary Care Physicians	Medical Geneticists	Genetic Counselors
Would give their opinion as to whether the woman should undergo prenatal diagnosis (vs refraining from giving their opinion)	1113 (43.8)*	141 (16.3)	139 (2.9)
Would give their opinion about pregnancy termination to a mother whose fetus was diagnosed with cystic fibrosis (vs refraining from giving their opinion)	1137 (9.6)†	141 (0.7)	139 (1.4)

*All three groups were significantly different from each other at $P < .0001$.

†Physicians were different from genetics professionals at $P < .0001$, but medical geneticists and genetic counselors did not differ from each other.

would discuss prenatal diagnosis with a carrier couple (49.4%) or refer them immediately to a genetic counselor (50.6%). Physicians were almost evenly divided in their willingness to give an opinion as to whether this carrier couple should undergo prenatal diagnosis (43.8% said yes, 56.2% said no). Surprisingly, there was no association between willingness to discuss prenatal diagnosis and willingness to give an opinion about prenatal diagnosis. That is, physicians who would discuss prenatal diagnosis were no more likely to give their opinions than those who would refer for prenatal diagnosis. Very few physicians (9.6%) indicated that they would give their opinions regarding pregnancy termination. Compared with either group of genetics professionals, physicians were significantly more likely to give their opinions about prenatal diagnosis; medical geneticists were more likely than genetic counselors to give their opinions (**Table 1**).

Physicians' willingness to discuss prenatal diagnosis and give their opinions differed by specialty. **Table 2** shows that obstetricians would be more likely than other specialists to refer a couple for prenatal ge-

netic counseling. Family practitioners would be more likely than obstetricians to discuss rather than refer for prenatal diagnosis. Psychiatrists would be the least likely to give an opinion about prenatal diagnosis, although this difference was not statistically significant. Compared with the other specialists, family practitioners and internists would be more likely to give their opinions about abortion.

CHARACTERISTICS ASSOCIATED WITH PHYSICIANS' PERCEPTIONS OF THEIR ROLE

As shown in **Table 3**, physicians who indicated that they would discuss prenatal diagnosis for CF with a carrier couple rather than refer the couple immediately to a genetic counselor were likely to have greater knowledge about genetics, greater confidence in communicating about genetics, and higher tolerance for ambiguity and were more likely to have graduated recently from medical school and to practice in a rural area. Gender and attendance at religious services were not associated with making referrals. We also determined that rural and urban physicians did not differ in their knowledge, confidence, tolerance for ambiguity, and year of graduation.

With respect to the likelihood that respondents would give their opinion about whether a couple should undergo prenatal diagnosis, gender was the only significant variable. Women were less likely than men to report that they would give an opinion. This was particularly true for female obstetricians ($\chi^2=8.5$, $P<.005$) and psychiatrists ($\chi^2=18.7$, $P<.00005$). There was no gender difference among pediatricians.

A relatively small percentage of respondents indicated that they would give an opinion regarding pregnancy termination. Of those who would offer an opinion ($N=112$), 58.9% would object to termination and 41.1% would recommend termination. Those offering an opinion were more likely to have low knowledge scores, low confidence scores, and low tolerance for ambiguity and were more likely to be male, to have graduated from medical school prior to 1971, and to

Table 2. Physicians' Perceptions of Their Role in Prenatal Genetic Counseling by Specialty

Specialty	No. of Physicians	Would Discuss Prenatal Diagnosis, %		Would Give an Opinion About Prenatal Diagnosis, %		Would Give an Opinion About Abortion, %	
		Discuss	Refer*	Yes	No*	Yes	No
Pediatricians	257	54.7	45.3	44.4	55.6	5.8	94.2
Family practitioners	211	56.4	43.6	42.6	57.4	16.4	83.6
Obstetricians	224	36.9	63.1	44.7	55.3	5.4	94.6
Internists	214	48.1	51.9	50.5	59.5	14.5	85.5
Psychiatrists	230	50.4	49.6	37.0	63.0	7.0	93.0
Total	1136	49.4	50.6	43.8	56.2	9.6	90.4

* $P < .0003$ by overall χ^2 analysis.

Table 3. Factors Associated With Physicians' Perceptions of Their Role in Prenatal Genetic Counseling

	No. of Physicians	Would Discuss Prenatal Diagnosis, %		Would Give an Opinion About Prenatal Diagnosis, %		Would Give an Opinion About Abortion, %	
		Discuss	Refer	Yes	No	Yes	No
Knowledge							
High	586	55.8*	44.2	42.9	57.1	6.6*	93.4
Low	543	42.5	57.5	44.7	55.3	12.7	87.3
Confidence							
High	629	53.1†	46.9	43.3	56.7	7.1†	92.9
Low	500	44.8	55.2	44.3	55.7	12.6	87.4
Tolerance for ambiguity							
High	536	53.4‡	46.6	44.3	55.7	7.8‡	92.2
Low	593	45.9	54.1	43.2	56.8	11.2	88.8
Gender							
Male	915	49.5	50.5	47.0†	53.0	10.7†	89.3
Female	222	49.1	50.9	30.6	69.4	5.0	95.0
Year of graduation							
1950-1970	365	38.4†	61.6	46.9	53.1	14.1†	85.9
1971-1985	764	54.7	45.3	42.3	57.7	7.4	92.6
Geographic area							
Rural	92	67.4*	32.6	50.5	49.5	11.8	88.2
Nonrural	1031	48.0	52.0	43.2	56.8	9.2	90.8
Religiosity							
Very important	230	47.8	52.2	41.7	58.3	20.6†	79.4
Not very important	890	49.9	50.1	44.3	55.7	6.8	93.2

* $P < .0005$.† $P < .005$.‡ $P < .05$.

indicate that attending religious services regularly is very important.

Table 4 shows the multiple regression analyses used to predict whether physicians would discuss prenatal diagnosis with their patients and whether they would give their opinions regarding pregnancy termination. (Multivariate analysis was not performed to predict whether physicians would give an opinion about prenatal diagnosis since gender was the only predictor variable associated with this outcome.) In the first model, the strongest predictor of whether physicians would discuss prenatal diagnosis was practicing in a rural area, followed by recent graduation, high knowledge score, high tolerance for ambiguity, and specializing in family practice as opposed to obstetrics. In the second model, physicians who would give their opinions regarding abortion were 3½ times more likely to value attendance at religious services, over 2½ times more likely to be internists or family practitioners than obstetricians, and more likely to have low confidence scores and to have graduated prior to 1971.

COMMENT

In this study we investigated primary care physicians' and psychiatrists' perceptions of their role in communicating about prenatal diagnosis for CF, a new genetic technology. Of major interest was the extent to which physicians would

Table 4. Logistic Regressions to Predict Physicians' Perceptions of Their Role in Discussing Prenatal Diagnosis and Giving Their Opinions About Abortion

	Logistic Regression Coefficient (SE)	Odds Ratio (95% Confidence Interval)	P
Discussing prenatal diagnosis			
High knowledge	.41 (.13)	1.5 (1.16-1.95)	.001
High tolerance for ambiguity	.30 (.12)	1.4 (1.06-1.72)	.01
Recent graduation	.53 (.14)	1.7 (1.28-2.25)	.0001
Rural setting	.65 (.24)	1.9 (1.19-3.09)	.008
Family practice*	.34 (.17)	1.4 (1.01-1.97)	.04
Giving their opinion about abortion*			
High confidence	-.54 (.21)	0.6 (0.38-0.72)	.01
Recent graduation	-.76 (.21)	0.5 (0.31-0.71)	.0004
Religiosity	1.3 (.22)	3.5 (2.36-5.7)	.00001
Family practice*	.95 (.25)	2.6 (1.57-4.26)	.0002
Internal medicine*	1.0 (.26)	2.8 (1.62-4.57)	.0001

*Obstetrics was the reference group for specialty in both regressions.

engage in genetic discussions (counsel) at all and would deviate from the tradition of nondirectiveness on which genetic counseling theoretically is based¹⁴ and that was supported by the attitudes of genetics professionals in this study.

COUNSELING ABOUT PRENATAL DIAGNOSIS VS REFERRING FOR COUNSELING

The results show that half of physicians would be willing to counsel about prenatal genetic testing and half would prefer to leave such discussions to genetics professionals. To the extent that respondents who were willing to discuss prenatal testing had higher genetics knowledge scores, were better able to tolerate ambiguity, and were educated more recently (and, therefore, perhaps were better able to appreciate the increasing importance of genetics in medicine), they were better qualified to counsel than those who would refer. Whether those who would counsel were adequately qualified cannot be answered by this study.

Respondents' willingness to discuss prenatal diagnosis is influenced by their specialty and by whether they practice in a rural area. Obstetricians are more likely than other specialists to refer their patients for counseling about prenatal diagnosis, perhaps because they have established connections with genetic counselors as a way of managing the demand for genetic services in their practice. Obstetricians may begin to do more counseling as they perform more of their own amniocenteses. That family practitioners would be more likely than obstetricians to discuss prenatal diagnosis may be partially explained by their greater likelihood of practicing in rural areas ($P < .00001$). It is reassuring to know that physicians in this study who practice in remote locations appear no less qualified (as measured by knowledge, tolerance for ambiguity, and year of graduation) to offer genetic services than those in urban areas.

WILLINGNESS TO GIVE OPINIONS REGARDING PRENATAL DIAGNOSIS AND ABORTION

Physicians were significantly more willing than medical geneticists and genetic counselors to give their opinions about prenatal diagnosis and abortion, and male physicians were more likely to do so than female physicians. A similar gender difference was found among genetics professionals ($P < .00001$). That genetic counselors would be even less likely than medical geneticists to give an opinion about prenatal diagnosis could be related to the fact that genetic counselors are predominantly female, or it could be related to their nondirective training.

Among primary care specialists, almost half of obstetricians (the specialists most involved in prenatal diagnosis) reported a willingness to give an opinion about prenatal diagnosis. Obstetricians were the least likely to give their opinions about abortion. Physicians who would give their opinions about abortion, although a minority, were more likely to attend religious services regularly and to come from specialties with less exposure to genetics (eg, internal medicine). The directiveness of those with less exposure to genetics could reflect less experience with genetics or a failure to distinguish reproductive issues from

other topics these physicians may discuss with their patients in a directive or authoritative manner. There is a need for further study of motivational differences between physicians who are willing to give their opinions and those who are not.

PHYSICIANS WHO give their opinions do not necessarily undermine autonomous decision making on the part of patients, especially if patients ask for their physician's opinion. Opinion seeking on the part of patients may occur more frequently in the context of long-term relationships with providers such as family practitioners than in the context of one-time contacts with genetics professionals. Many physicians and patients believe that it is appropriate and desirable for physicians to give advice to patients. Some believe that as long as physicians acknowledge their biases and uncertainties, their giving advice to patients is consistent with respect for patient autonomy unless the patient is unduly influenced. How and in what context physicians give their opinions may be of greater importance than whether they do so.

There is considerable controversy about when, if ever, it is appropriate to give opinions to patients when communicating about genetic testing. One view says that the practitioner's opinion should never be given in any context because genetic decisions are inherently value-laden and the perception of practitioners (especially male physicians¹³) as powerful can influence patients to behave in ways that are not consistent with their own values. This view provides the basis of value neutrality in genetic counseling. Another view says that giving opinions is inappropriate only in the context of reproductive genetic counseling, where decisions about conception and abortion are implicated. A third view says that the appropriateness of the practitioner's opinion regarding genetic testing depends on whether there is a beneficial treatment that can be offered. For example, when presymptomatic genetic testing for familial colon cancer is available, physicians would be remiss in not recommending testing, as colectomy can be beneficial to people who carry the gene. In such cases, genetic decisions are no different than other medical decisions in which physicians are expected to give their advice. In contrast, if no effective treatment is available (eg, Huntington's disease), it is difficult to justify recommending presymptomatic testing.

Although it is a matter of some debate whether the tradition of nondirectiveness espoused by genetics professionals is real and not rhetorical,⁶ at the very least, value neutrality and nondirective counseling have been the prevailing "ideals." Our findings suggest that the ethos regarding patient counseling may be different for many primary care physicians, and as these physicians become more involved in genetic counseling, the extent of directiveness may change.

LIMITATIONS AND FUTURE RESEARCH

The validity and generalizability of these results may be affected by several limitations. First, there may be a tendency for respondents to provide socially desirable answers. Given that a substantial number of respondents admitted a tendency to give an opinion and that many more are likely to give their opinions without acknowledging it, our findings are likely to reflect a conservative estimate of the tendency of physicians to be directive.

Second, our findings may not be representative of all physicians. For example, the facts that we oversampled younger physicians, that younger physicians were more likely to respond, and that younger physicians appear more likely than older graduates to discuss prenatal diagnosis suggest that we might be overestimating the degree to which physicians in the general population would counsel about prenatal diagnosis. Similarly, the fact that younger physicians appear less likely than older graduates to give their opinions about abortion suggests that our findings may underestimate the degree to which physicians in the general population are directive about abortion. Younger physicians may be more aware of the sensitivity of the abortion issue or may be trained to be less directive in general than physicians in years past. Alternatively, young physicians may become more directive as they are in practice longer. These are empirical questions that warrant prospective study.

Third, this study is limited by the hypothetical nature of the scenario and the focus on CF. Both are likely to have put psychiatrists and internists at a disadvantage. These specialists have not had much experience in offering genetic services of any kind, least of all prenatal genetic testing. We are unable to generalize from the responses of psychiatrists and internists about how they might respond to the availability of DNA testing for common adult diseases, such as familial Alzheimer's disease and colon cancer, respectively. If the future demands that these specialists have a clear role in genetic testing for adult-onset diseases, some form of postgraduate training or continuing medical education may be needed to provide them with opportunities to learn about genetics and counseling.

Subsequent research should evaluate specialty- and gender-specific attitudes toward genetic interventions and should incorporate qualitative data-collection methods, such as individual interviews, focus groups, and audiotaped patient encounters. Such studies would provide a more accurate picture of how various primary care specialties are likely to respond to and communicate about

new genetic tests and would enable us to assess the effect of other influences, such as their attitudes toward abortion. By achieving a better understanding of how physicians will incorporate new genetic technologies into primary care practice, we can enable appropriate, safe, effective, and equitable use of these technologies.

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Dr. HOLTZMAN. Work of the type I have just described, supported by the Human Genome Project, is helping this country chart a safer course in the pathway from discovery of genes to routine use of genetic tests. The National Center for Human Genome Research, in cooperation with other institutes at NIH, has provided support to several medical centers to establish pilot programs for cystic fibrosis carrier screening and to other centers to explore issues in testing for hereditary breast, ovarian, and colon cancer.

NIH and DOE also supported the convocation of an Institute of Medicine Committee that you heard about from Dr. Patrinos to consider ethical, legal, and social implications of genetic testing. I was a member of that committee and again, with your permission, would like to enter the executive summary into the committee's record.

Mrs. LLOYD. Without objection.

[The information follows:]

EXECUTIVE SUMMARY

**ASSESSING
GENETIC RISKS**

**IMPLICATIONS FOR HEALTH
AND SOCIAL POLICY**

Lori B. Andrews, Jane E. Fullarton,
Neil A. Holtzman, and Arno G. Motulsky, *Editors*

Committee on Assessing Genetic Risks
Division of Health Sciences Policy
Institute of Medicine

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NOTICE: The project that is the subject of this report was approved by the Governing Board of the National Research Council, whose members are drawn from the councils of the National Academy of Sciences, the National Academy of Engineering, and the Institute of Medicine. The members of the committee responsible for the report were chosen for their special competencies and with regard for appropriate balance.

This report has been reviewed by a group other than the authors according to procedures approved by a Report Review Committee consisting of members of the National Academy of Sciences, the National Academy of Engineering, and the Institute of Medicine.

The Institute of Medicine was chartered in 1970 by the National Academy of Sciences to enlist distinguished members of the appropriate professions in the examination of policy matters pertaining to the health of the public. In this, the Institute acts under both the Academy's 1863 congressional charter responsibility to be an adviser to the federal government and its own initiative in identifying issues of medical care, research, and education. Dr. Kenneth I. Shine is president of the Institute of Medicine.

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This Executive Summary is available in limited quantities from the Institute of Medicine, Committee on Assessing Genetic Risks, 2101 Constitution Avenue, N.W., Washington, D.C. 20418.

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The serpent has been a symbol of long life, healing, and knowledge among almost all cultures and religions since the beginning of recorded history. The image adopted as a logotype by the Institute of Medicine is based on a relief carving from ancient Greece, now held by the Staatliches Museum in Berlin.

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Preface

The last decade has seen remarkable growth in the understanding of genetics as applied to medicine. In addition, the technology for the detection of genetic diseases has developed rapidly, and testing for genetic diseases with DNA techniques has become increasingly possible. The last few years have also seen the initiation of the Human Genome Project, the aim of which is mapping and ultimately sequencing all human genes—giving special attention to genes that cause or may predispose to disease. As part of this ambitious project, and for the first time in the history of science, a special effort is being made as part of a large research project to explore its broader social implications. Three to five percent of the funding available for the Human Genome Project has been set aside to study the many social, ethical, and legal implications that will result from better understanding of human heredity and its impact on disease. Since assessment of genetic risks by genetic testing is expanding rapidly, the Institute of Medicine (IOM) of the National Academy of Sciences undertook this study to assess the current status and future implications of such testing. This study deals with some of the scientific aspects of genetic risk assessment as well as the many societal problems that have already arisen and are likely to be posed by future developments. The study was supported jointly by the National Center for Human Genome Research at the National Institutes of Health and by the Department of Energy, Health Effects Program of the Life Science Research Office. Supplemental funding was provided by the Markey Charitable Trust, a private foundation, and these funds were matched by the Institute of Medicine.

A multidisciplinary Committee on Assessing Genetic Risks was constituted and held a series of workshops and meetings (including a public meeting) on the

many phases of genetic testing and its impact on patients, providers, and laboratories. Based on the information gleaned from the many expert participants in these workshops, the public, the appropriate scientific and policy literature, and extensive discussions at committee meetings, the report was written. As part of its process, the committee had the benefit of a Liaison Panel whose members had industrial relationships. This panel worked with the committee during the information gathering activities; once recommendations and report writing began, the liaison members no longer participated.

The rapidly changing nature of the science and practice of genetic testing has led the committee to approach its recommendations by providing general principles that we hope will be useful today and for the next few years. We tried, whenever possible, to avoid technical complexities without sacrificing scientific accuracy to make our conclusions available to as large an audience as possible.

Our committee hopes that this report will be widely read, not only by various health professionals interested in genetics and medicine, but by a broad audience who makes and influences public policy, such as federal and state legislators, other officials and their staff, members of genetic support groups, and the public. Health professionals, an interested public, and policy makers will need to be well informed to move forward with thoughtful and judicious decision making in this area. These recommendations must be based on solid facts and, at the same time, recognize and respect the multifaceted aspects of our pluralistic society. These recommendations are the result of carefully considered judgment, based on a careful review of the state of the art of genetic testing today and our vision of the future. Since currently no single voice has the authority to make policy recommendations in the field of genetic risk assessment and testing, it is hoped the findings of this broadly based multidisciplinary IOM committee will serve as a set of recommendations on which future decisions can be based.

We addressed the need for better professional training of health professionals and of human and medical geneticists. Many genetic tests will be ordered and interpreted by primary care health practitioners, and not only by geneticists or genetic counselors. A good understanding of genetics will therefore be required for all health care professionals. A movement of genetic testing from academic institutions to commercial laboratories is taking place already and will increase as larger volumes of genetic tests are being ordered. The regulation of laboratories sufficiently expert to carry out genetic testing as well as quality control of testing takes on great importance and we have developed a series of recommendations on these important matters.

Various health care providers and medical geneticists already have considerable experience with newborn screening, with prenatal diagnosis, with carrier testing in high-risk populations, and with testing for a variety of genetic diseases. However, the development of genetic tests for diseases that manifest in middle and late life is just beginning to be explored. It is in this area that much new ground needs to be covered. While interpretation of tests for single gene disorders

of late onset, including familial cancer, is not easy, the complexities of testing and interpretations for the gene constellations that predispose to many common diseases such as coronary heart disease, diabetes mellitus, hypertension, and others raise new problems. These dilemmas will become particularly thorny if testing for the yet undiscovered genes predisposing to common psychiatric diseases such as schizophrenia and manic depressive disorders becomes a reality.

Testing of DNA from various body tissues for the early mutational events that predispose to a variety of common cancers is on the horizon. This area of genetic testing promises to revolutionize early cancer detection and poses many problems of health monitoring.

Many issues raised by genetic testing do not have a single or unambiguous solution, and different well-informed and well-meaning observers may disagree with each other. Public health oriented policy makers, many physicians, and a significant proportion of the public might consider the reduction of genetic disease as a principal goal of work in this area. Our committee stressed the importance of autonomous decision making by individuals and by the family even if the development of a genetic disease might be the outcome. We believe that in a society such as ours, autonomy far outweighs any public health considerations. In practice, most informed couples do, in fact, select various courses of actions that lead to a lower frequency of genetic disease.

There is a strong and continuing tradition of nondirective genetic counseling in medical genetics, and we were emphatic in stressing nondirectiveness. However, impressed by medical advances that can lead to prevention and treatment of some genetic diseases, many of us feel that there is an obligation under such circumstances to provide appropriate medical advice with guidance to select a specific preventive or therapeutic course of action after a full discussion of all consequences (including possible insurance repercussions and employment discrimination). At the same time, all committee members strongly uphold the principle of nondirective counseling for *reproductive* decisions.

Arno G. Motulsky, M.D., Sc.D.
Chair

ADDITIONAL VIEWS OF THE CHAIRMAN*

Our report may strike some observers as emphasizing the problematic aspects of genetic testing. All members of the Committee on Assessing Genetic Risks are excited about the great promise and potential of genetic testing for the prevention and treatment of genetic diseases. Since the positive aspects of genetic testing are clear, this perspective required less explication. Our report, therefore, covers in

*The opinions expressed are my own and do not represent the consensus of a majority of the committee.

some detail the difficulties raised by genetic testing and screening, and suggests some solutions and guidelines.

Our emphasis on genetic education may be considered somewhat utopian when an increasing proportion of the population is illiterate and dropout rates in high schools are rising. Nevertheless, we feel that an understanding of genetics will be most important in the future, not only for an appreciation of the role of genetics in health and disease, but also for making decisions on issues such as the use of foods developed with DNA technologies. Even though we may not be able to educate everyone, much more intensive coverage of genetics in the schools at all levels, as well as responsible reporting in the media, is something to which all of us strongly subscribe.

The recommendations regarding newborn screening represent somewhat ideal scenarios that may require some modification in practice. For example, even though full genetic education and counseling would be ideal prior to newborn screening, such a practice may not be currently realistic. For every single affected infant, there will be many thousands of unaffected children. Pretest education and counseling in such a situation cannot, by necessity, be as comprehensive as in scenarios where the pretest probability for a child to be affected is high. However, once a child is found to be affected, equally intensive counseling and appropriate follow-up are indicated in both situations.

The majority of our committee was persuaded that voluntary participation in neonatal screening was the best way to ensure that children would be screened and parental autonomy maintained. Everyone agreed that testing should always be offered for phenylketonuria (PKU) and hypothyroidism since early treatment is highly successful. Some committee members feel that mandatory screening for these two conditions would be a simpler solution.

The common, medically innocuous sickle cell trait will frequently be detected in African-American children as a side product of newborn testing for sickle cell anemia. Once this knowledge—with its significant reproductive implications for the parents—is available, such information is difficult to withhold and in my opinion should be given to the mother with appropriate genetic counseling.

There is agreement that information regarding carrier status of a medically innocuous genetic trait should not be used to discriminate against a child being considered for adoption. However, once a disease has been diagnosed or if there is a high risk of a medically significant condition, I believe strongly that prospective adoptive parents should be provided this information.

Arno G. Motulsky, M.D., Sc.D.
Chair

Acknowledgments

In addition to the work of the committee and staff, the successful completion of a study such as this requires assistance from many people. The committee wishes to express its sincere gratitude to those who participated in and prepared papers for the workshops and public forum (see Appendix A and Volume 2). The committee also wishes to thank those who prepared background papers: David A. Micklos, Director of the DNA Learning Center at the Cold Spring Harbor Laboratory, for his paper on issues in public education (Volume 2); Ann C. M. Smith for her background paper on professional personnel issues prepared in collaboration with Jane Fullarton and C. Elaine Lawson of the committee staff; and Kathi E. Hanna who contributed background papers on genetic testing and genetic counseling, as well as material on personnel issues.

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This report includes a number of recommendations that the committee hopes will achieve the goal of acquiring and using genetic information in health care in a manner that respects the autonomy of individuals.

Genetic testing may raise complex or novel questions about the right to access information, and these questions may have legal ramifications. This report should not be interpreted as creating a set of legal guidelines. Relevant laws and regulations will vary from state to state. Clinicians or other persons who have questions about the appropriate management of genetic information may on occasion wish to consider seeking legal counsel.

Executive Summary

Approximately 3 percent of all children are born with a severe disorder that is presumed to be genetic in origin, and several thousand definite or suspected single-gene diseases have been described. Most of these diseases manifest themselves early in life, although some inherited diseases—and many others that have a genetic component—have their onset much later in life (e.g., diabetes mellitus or mental illness). Then there are many disorders in which both genetic and environmental factors play major roles (e.g., coronary heart disease, hypertension). These “complex” disorders are more common than single-gene diseases and thus, in the aggregate, constitute a greater public health burden. Many disease genes can be detected in individuals before symptoms occur, but for many common diseases with some genetic basis, such as heart disease and cancer, the detection of genetic alterations might only indicate susceptibility, not the certainty of disease.

PROMISE AND PROBLEMS IN GENETIC TESTING

The ability to diagnose genetic disease has developed rapidly over the past 20 years, and the Human Genome Project, with its ambitious goal of mapping and sequencing the entire genome, will bring a further explosion in our knowledge of the structure and function of human genes. The ultimate goals of these scientific advances are the treatment, cure, and eventual prevention of genetic disorders, but effective interventions lag behind the ability to detect disease or increased susceptibility to disease. Thus, many genetic services today consist of diagnosis and counseling; effective treatment is rare. Nevertheless, as more genes are identi-

fied, there is growing pressure to broaden existing screening programs, and otherwise increase both the number of available genetic tests and the volume of genetic information they generate.

The rapidly changing science and practice of genetic testing raise a number of scientific, ethical, legal, and social issues. The national investment in the Human Genome Project will greatly increase the capacity to detect genes leading to disease susceptibility. It will also greatly increase the availability of genetic testing over the next 5 to 10 years, identifying the genetic basis for diseases—even some newly discovered to be genetic—and increasing the number of tests for detecting them. The emergence of the biotechnology industry increases the likelihood that these findings will be rapidly translated into widely available test kits and diagnostic products. Entrepreneurial pressure may also lead to the development of commercial and academic “genetic testing services” that would not be regulated under current Food and Drug Administration (FDA) procedures. Problems of laboratory quality control would be heightened by the introduction of “multiplex” tests that detect the presence of numerous genetic markers—for disease, carrier status, and susceptibility alike—at the same time. And the potential for generating all of this genetic information about individuals raises serious questions of informed consent, confidentiality, and discrimination. Over the next five to ten years, there will be an increasing number of personal and public policy decisions related to genetic testing; well-trained health professionals and an interested and informed public will both be key to that decision making.

As genetic screening becomes more widespread, these issues threaten to out-run current ethical and regulatory standards, as well as the training of health professionals. There will be a need for greater numbers of genetics specialists, but genetic testing is no longer just for specialists. Increasingly, primary care providers will be called upon to administer tests, counsel patients, and protect their privacy. Government officials and the broader public will also be called upon to participate in setting public policy for genetic testing and in making difficult decisions, public and private, based on the results of genetic tests. Consequently, there must be a significant increase in genetics education, both in the medical curriculum and for all Americans. Finally, there will be a need for centralized oversight to ensure that new genetic tests are accurate and effective, that they are performed and interpreted with close to “zero-error” tolerance, and that the results of genetic testing are not used to discriminate against individuals in employment or health insurance.

COMMITTEE ON ASSESSING GENETIC RISKS

This study of the scientific, ethical, legal, and social issues implicit in the field of genetic diagnosis, testing, and screening was supported jointly by the National Center for Human Genome Research at the National Institutes of Health and the Department of Energy’s Health Effects and Life Sciences Research Of-

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fice. Supplemental funding was also provided by the Markey Charitable Trust and the Institute of Medicine. The Committee on Assessing Genetic Risks hopes that this report will be widely read, not only by various health professionals interested in genetics and preventive medicine, but by a wide-ranging audience who makes and influences public policy in the United States, including members of genetic support groups and the public.

The establishment of the Ethical, Legal, and Social Implications (ELSI) Program in the Human Genome Project (HGP) and the set-aside of the first 3 to 5 percent of the HGP research budget for the study of ethical, legal, and social issues is unique in the history of science. This support gives us the opportunity to "worry in advance" about the implications and impacts of the mapping and sequencing of the human genome, including several thousand human disease genes, *before* wide-scale genetic diagnosis, testing, and screening come into practice, rather than *after* the problems have presented themselves in full relief.

The committee took its starting point from the wise advice of the 1975 National Academy of Sciences study *Genetic Screening: Programs, Principles, and Research*:

Screening programs for genetic diseases and characteristics . . . have multiplied rapidly in the past decade, and many have been begun without prior testing and evaluation and not always for reasons of health alone. Changes in disease patterns and a new emphasis on preventive medicine, as well as recent and rapid advances in genetics, indicate that screening for genetic characteristics will become more common in the future. These conditions, together with the mistakes already made, suggested the need for a review of current screening practices that would identify the problems and difficulties and give some procedural guidance, in order to minimize the shortcomings and maximize the effectiveness of future genetic screening programs.

These words, written almost 20 years ago, remain just as valid today for genetic testing and diagnosis. The committee reaffirms the sentiments expressed in the 1975 report and hopes to update and broaden their application for the 1990s and beyond.

As a result, the committee has posed its recommendations in terms of general principles that we hope will be useful today—and for some years into the future—for the evaluation of expanded genetic diagnosis, testing, and screening. Although these recommendations reflect what is known today, and what experts foresee for the next few years, the committee had no crystal ball and, therefore, tried to develop criteria and to suggest processes for assessing when new tests are ready for pilot introduction and for widespread application in the population.

The committee's fundamental ethical principles include *voluntariness, informed consent, and confidentiality*, which in turn derive from respect for autonomy, equity, and privacy. Other committee principles described in the report include the necessity of (1) *high-quality tests (of high specificity and sensitivity)*

performed with the highest level of proficiency and interpreted correctly; and (2) conveying information to clients—both before and after testing—in an easily understood manner through genetic education and counseling that is relevant to the needs and concerns of the client. These principles are the absolute foundation of genetic testing.

It is the view of the committee that, *until benefits and risks have been defined, genetic testing and screening programs remain a form of human investigation.* Therefore, routine use of tests should be preceded by pilot studies that demonstrate their safety and effectiveness. Standard safeguards should be applied in conducting these pilot studies, and independent review of the pilot studies should be conducted to determine whether the test should be offered clinically. Publicly supported population-based screening programs are justified only for disorders of significant severity, impact, frequency, and distribution, and when there is consensus that the available interventions warrant the expenditure of funds. **Informed consent should be an essential element of all screening. These principles and procedures described above should apply to genetic testing regardless of the setting, whether in primary medical practice, public programs, or any other settings.**

GENETIC TESTING AND ASSESSMENT

Genetic tests include the many different laboratory assays used to diagnose or predict a genetic condition or the susceptibility to genetic disease. *Genetic testing* denotes the use of specific assays to determine the genetic status of individuals already suspected to be at high risk for a particular inherited condition because of family history or clinical symptoms; *genetic screening* involves the use of various genetic tests to evaluate populations or groups of individuals independent of a family history of a disorder. However, these terms are commonly used interchangeably, and the committee has generally used the term *genetic testing* unless a specific aspect of genetic screening alone is being discussed. *Genetic counseling* refers to the communication process by which individuals and their family members are given information about the nature, recurrence risk, burden, risks and benefits of tests, and meaning of test results, including reproductive options of a genetic condition, as well as counseling and support concerning the implications of such genetic information.

Newborn Screening

At the present time, there are 10 genetic conditions for which some states screen newborns, although the scope of such screening varies by state (see Table 1). It is also possible to extract DNA from the newborn blood “spots” that are used for these tests. There is increasing pressure to test old blood samples for a wide variety of disorders, as well as to do DNA testing on newborns for a wide

TABLE 1 Genetic Disorders for Which Newborns Were Screened in the United States in 1990

Disorder	No. of States That Provided Screening ^a
Phenylketonuria	52
Congenital hypothyroidism ^b	52
Hemoglobinopathy	42 ^c
Galactosemia	38
Maple syrup urine disorder	22
Homocysteinuria	21
Biotinidase deficiency	14
Adrenal hyperplasia	8
Tyrosinemia	5
Cystic fibrosis	3 ^d

^aIncludes District of Columbia, Puerto Rico, and U.S. Virgin Islands.

^bOnly a proportion of cases have a genetic etiology.

^cUtah's hemoglobinopathy pilot study (6-1-90 through 3-31-91) has been discontinued.

^dWisconsin's cystic fibrosis screening program is for research purposes only.

SOURCE: Council of Regional Networks for Genetic Services, 1992.

variety of disorders in the future. **As basic principles to govern newborn screening, the committee recommends that such screening take place only when (1) there is a clear indication of benefit to the newborn, (2) a system is in place to confirm the diagnosis, and (3) treatment and follow-up are available for affected newborns.** In addition, the committee does not believe that newborns should be screened using multiplex testing for many disorders at one time unless all of the disorders meet the principles described by the committee in this report (see Chapters 2 and 8).

To determine clear benefit to the newborn, well-designed and peer-reviewed pilot studies are required to demonstrate the safety and effectiveness of the proposed screening program. In pilot studies for new population-based newborn screening programs, parents should be informed of the investigational nature of the test and have the opportunity to consent to the participation of their infant. **Since some existing programs may not have been subject to careful evaluation, the committee recommends that ongoing programs be reviewed periodically, preferably by an independent body that is authorized to add, eliminate, or modify existing programs** (see Chapters 1, 3, and 9). The need for ongoing review and revision also suggests that detailed statutory requirements for specific tests may be unduly inflexible; state statutes should provide guidance for standards—not prescriptions. **The committee recommends that states with newborn screening programs for treatable disorders also have programs**

available to ensure that necessary treatment and follow-up services are provided to affected children identified through newborn screening without regard to ability to pay. Informed consent should also be an integral part of newborn screening, including disclosure of the benefits and risks of the tests and treatments. Finally, mandatory screening has not been shown to be essential to achieve maximum public health benefits; however, it is appropriate to mandate the *offering* of established tests (e.g., phenylketonuria, hypothyroidism) where early diagnosis leads to improved treatable outcomes. (See Chapter 8.)

Newborns should not be screened for the purpose of determining the carrier status of the newborn or its parents for autosomal recessive disorders. Instead, couples in high-risk populations who are considering reproduction should be offered carrier screening for themselves (see below). When carrier status may be incidentally determined in newborn screening (e.g., in sickle cell screening), parents should be informed in advance about the benefits and limitations of genetic information, and that this information is not relevant to the health of their child. If they ask for the results of the incidentally determined carrier status for their own reproductive planning, it should be communicated to them in the context of genetic counseling, and they should be informed that misattributed paternity could be revealed. **Newborn screening programs should include provision for counseling of parents who are informed that the child is affected with a genetic disorder.**

The committee recognizes the complexities of identifying information about misattributed paternity. **On balance, the committee recommends that information on misattributed paternity be communicated to the mother, but not be volunteered to the woman's partner.** There may be special circumstances that warrant such disclosure, but these situations present difficult counseling challenges (see Chapters 4 and 8).

Stored newborn blood spots should be made available for additional research only if identifiers have been removed. As with other research involving human subjects, research proposals for the subsequent use of newborn blood spots should be reviewed by an appropriate institutional review board. If identifiable information is to be disclosed, informed consent of the infant's parent or guardian should be obtained prior to use of the specimen (see Chapters 2 and 8 for further discussion). Although DNA typing will provide new tools for newborn screening, in general, the committee recommends that these tools be employed only (1) when genetic heterogeneity of conditions to be detected is small; (2) when the sensitivity of detecting disease-causing mutations is high; (3) when costs are reasonable; and (4) when the benefits to newborns of early detection are clear.

Carrier Identification

Carrier testing is usually provided for purposes of reproductive planning. **The committee recommends that couples in high-risk populations who are**

considering reproduction be offered carrier screening before pregnancy if possible. Standard safeguards such as institutional review and demonstrated safety and effectiveness should be applied in initiating any carrier detection program. First, the test should be accurate, sensitive, and specific. In the future, such screening will be done increasingly as part of routine medical care; the same principles should apply regardless of the setting. Carrier testing and screening should also be voluntary, with high standards of informed consent and attention to telling individuals or couples, in easily understood terms, the medical and social choices available to them should they be found at risk for disease in their offspring, including termination of the pregnancy. Research is needed to develop innovative methods for providing carrier testing in young adults before pregnancy and to evaluate these methods through pilot studies. The committee had reservations about carrier screening programs in the high school setting in the United States and about carrier screening of persons younger than age 18.

With improving technology, carrier status for many different rare autosomal and X-linked recessive disorders will be detectable by multiplex technology (see Chapters 1 and 8). Obtaining appropriate informed consent before testing for each of these disorders will be a challenge (see Chapter 4). **Multiplexed tests should, therefore, be grouped into categories of tests (and disorders) that raise similar issues and implications for informed consent and for genetic education and counseling** (see Chapters 1, 4, and 8). If carrier status is detected, individuals should be informed of their carrier status to allow testing and counseling to be offered to their partners. Usually, the partner will be found not to be a carrier; however, if both partners are carriers, they should be referred for genetic counseling to help them understand available reproductive options, including the possibility of abortion of an affected fetus identified through prenatal diagnosis.

Prenatal Diagnosis

Anyone considering prenatal diagnosis must be fully informed about the risks and benefits of both the testing procedure and the possible outcomes, as well as alternative options that might be available. Disclosure should include full information concerning the spectrum of severity of the genetic disorders for which prenatal diagnosis is being offered (e.g., cystic fibrosis or fragile X). Furthermore, invasive prenatal diagnosis is only justified if the diagnostic procedures are accurate, sensitive, and specific for the disorder(s) for which prenatal diagnosis is being offered. **Standards of care for prenatal screening and diagnosis should also include education and counseling before and after the test, either directly or by referral, and ongoing counseling should also be available following termination of pregnancies.**

The committee believes that *offering* prenatal diagnosis is an appropriate standard of care in circumstances associated with increased risk of carrying a fetus with a diagnosable genetic disorder, including the increased risks associated

with advanced maternal age. However, the committee was concerned about the use of prenatal diagnosis for identification of trivial characteristics or conditions. **It was the consensus of this committee that prenatal diagnosis should only be offered for the diagnosis of genetic disorders and birth defects.** A family history of a diagnosable genetic disorder warrants the offering of prenatal diagnosis, regardless of maternal age, as does determination of carrier status in both parents of an autosomal recessive disorder for which prenatal diagnosis is available. Prenatal diagnostic services for detection of genetic disease for which there is a family history should be reimbursed by insurers (see Chapters 2 and 7). Ability to pay should not restrict appropriate access to prenatal diagnosis or termination of pregnancy of an affected fetus.

The committee felt strongly that the use of fetal diagnosis for determination of fetal sex and the subsequent use of abortion for the purpose of preferential selection of the sex of the fetus represents a misuse of genetic services that is inappropriate and should be discouraged by health professionals. More broadly, reproductive genetic services should not be used to pursue eugenic goals, but should be aimed at increasing individual control over reproductive options. As a consequence, additional research is needed on the impact of prenatal diagnosis, particularly its immediate and long-term impact on women, and on the design and evaluation of genetic counseling techniques for prenatal diagnosis for the future.

Testing for Late-Onset Disorders

Science is moving closer to defining the genetics of such adult disorders as Alzheimer disease, a variety of cancers, heart disease, and arthritis, to name a few (see Chapter 2). A combination of genetic and environmental factors plays a predominant role in most people afflicted with these disorders, but we do not yet understand why some people with a certain gene(s) develop a disease and others do not. Although further work may eventually elucidate the gene(s) involved, there may be long delays until the time when effective interventions are available for many disorders. Furthermore, not all affected individuals will have an identifiable genetic basis to their disorder. Thus, the complexities involved in determining and establishing susceptibility, sorting out potential environmental influences, and devising a strategy for counseling and treatment will pose tremendous challenges in the future.

Many of these diseases do not manifest clinically until adulthood and may become apparent only in middle age or later. *Predictive or presymptomatic* testing and screening can provide clues about genetic susceptibility or predisposition to genetic disorders. For monogenic disorders of late onset, such as Huntington disease, tests will usually be highly predictive. Many common diseases usually have multifactorial—or complex—causation, including both multiple genetic factors and environmental effects; for these disorders, prediction will be less certain.

Many common diseases of adulthood, including coronary artery disease, some cancers, diabetes, high blood pressure, rheumatoid arthritis, and some psychiatric diseases, fall into this category. However, in rare forms of these common diseases, single genes may play the decisive role; screening for disease-causing alleles of these genes will be of much greater predictive value.

The committee therefore recommends caution in the use and interpretation of presymptomatic or predictive tests. The nature of these predictions will usually be probabilistic (i.e., with a certain degree of likelihood of occurrence) and not deterministic (i.e., not definite, settled, or without doubt). The dangers of stigmatization and discrimination are areas of concern, as is the potential for harm due to inappropriate preventive or therapeutic measures. Since environmental factors are often essential for the manifestation of complex diseases, the detection of those at high risk will identify certain individuals who will most benefit from certain interventions (e.g., dietary measures in coronary heart disease). Identification of some persons at high risk for certain cancers suggests that more frequent monitoring may identify the earliest manifestations of cancer when treatability is greatest (e.g., colon cancer); research is needed on the psychosocial implications of such testing in both adults and children.

Further research and the unfolding of the Human Genome Project are likely to reveal the underlying genes mediating predisposition to numerous common diseases, and genetic susceptibility testing will be increasingly possible. Certain environmental factors may interact with only one set of genes and not with another. There may also be interaction between the various genes involved, so that the effects of multiple gene action cannot be predicted by separate analyses of each of the single genes. In such cases, definitive prediction will rarely, if ever, be possible. When dealing with genetic testing for some non-Mendelian diseases, it will be impossible to group individuals into two distinct categories—those at no (or very low) risk and those at high risk. Extensive counseling and education will be essential in any testing for genetic susceptibility. The benefits of the various presymptomatic interventions must be weighed against the potential anxiety, stigmatization, and other possible harms to individuals who are informed that they are at increased risk of developing future disease.

Population screening for predisposition to late-onset monogenic diseases should only be considered for treatable or preventable conditions of relatively high frequency. Under such guidelines, population screening should only be offered after appropriate, reliable, sensitive, and specific tests become available. Such tests do not yet exist. The committee recommends that the predictive value of genetic tests be thoroughly validated in prospective studies of sufficient size and statistical power before their widespread application. Since there will be a considerable time lag before the appearance of confirmatory symptoms, these studies will require support for long periods of time (see Chapter 3).

In the case of predictive tests for mental disorders, results must be handled with stringent attention to confidentiality to protect an already vulnera-

ble population. If no effective treatment is available, testing may not be appropriate since more harm than good could result from improper use of test results. On the other hand, future research might result in psychological or drug treatments that could prevent the onset of these diseases. Carefully designed pilot studies should be conducted to determine the effectiveness of such interventions and to measure the desirability and psychosocial impact of such testing. Interpretation and communication of predictive test results in psychiatry will be particularly difficult. To prepare for the issues associated with genetic testing for psychiatric diseases in the future, psychiatrists and other mental health professionals will need more training in genetics and genetic counseling; such training should include the ethical, legal, and social issues in genetic testing.

Because of their wide applicability, it is likely there will be strong commercial interests in the introduction of genetic tests for common, high-profile complex disorders. **Strict guidelines for efficacy therefore will be necessary to prevent premature introduction of this technology.**

Testing of Children or Minors

Children should generally be tested only for genetic disorders for which there exists an effective curative or preventive treatment that must be instituted early in life to achieve maximum benefit. Childhood testing is not appropriate for carrier status, untreatable childhood diseases, and late-onset diseases that cannot be prevented or forestalled by early treatment. In general, the committee believes that testing of minors should be discouraged unless delaying such testing would reduce benefits of available treatment or monitoring. It is essential that the individual seeking testing understand the potential abuse of such information in society, including in employment or insurance practice, and that the provider should ensure that confidentiality is respected (see Chapter 8 for discussion of disclosure to relatives).

Because only certain types of genetic testing are appropriate for children, multiplex testing that includes tests specifically directed to obtaining information about carrier status, untreatable childhood diseases, or late-onset diseases should not be included in the multiplex tests offered to children. **Research should be undertaken to determine the appropriate age for testing and screening for genetic disorders, both to maximize the benefits of therapeutic intervention and to avoid the possibility of generating genetic information about a child when there is no likely benefit and there is possibility of harm to the child.**

LABORATORY ISSUES IN GENETIC TESTING

The committee's review of laboratory issues in genetic testing included a workshop with the nation's experts in laboratory quality assurance in genetic testing and meetings with federal officials responsible for implementing federal reg-

ulations under the Clinical Laboratory Improvement Amendments of 1988 (CLIA88) and the medical devices legislation under which the Food and Drug Administration regulates genetic testing products such as test kits, probes, and reagents. **The committee found that although adequate legislative authority exists to oversee the quality of genetic testing, this authority is not in fact being implemented for genetic testing.** For example, existing CLIA88 regulations could ensure the quality of genetic laboratory testing, but these regulations are not being applied to genetic testing at all. Similarly, FDA has authority to regulate genetic testing kits and associated genetic test reagents and DNA probes, but such tests are rarely being submitted to FDA for approval.

The safety and effectiveness of genetic tests should be established before they are used routinely and, even when that comes to pass, great care should be taken in performing the tests and interpreting the results. The committee is concerned that the regulatory burden not impede further development of tests or the offering of genetic testing services by laboratories; nevertheless, the committee believes that the nature of genetic tests and their interpretation, and the magnitude of the personal and clinical decisions that may be made based on those results—including the abortion of affected fetuses—warrant a standard with close to “zero” chance of error for such tests. Consequently, laboratories and personnel performing these tests should participate in proficiency testing programs, including review of the interpretation provided by the laboratory to referring physicians. Laboratories with any error should be placed on probation, and proficiency testing repeated, preferably using blinded methods. Unless the laboratory can attain this standard, its certification to perform this test should be removed.

Existing quality assurance in genetic testing is voluntary and has improved laboratory quality in its participants, but the committee finds that current laboratory quality control programs are inadequate to address the special issues posed by genetic testing primarily because these programs lack essential enforcement authority. As genetic testing expands, these voluntary programs should and will be replaced by the requirements of CLIA88. **In the interim, the committee believes that the impact of voluntary programs could be strengthened by publishing the names of laboratories that have satisfied proficiency and other requirements.** This is now done by the National Tay-Sachs Disease and Allied Disorders Association, Inc., which publishes results of the quality assessment conducted by the International Tay-Sachs Disease Quality Control Reference Standards and Data Collection Center. Before publication, any laboratory not satisfying these requirements should be given ample opportunity to rectify its deficiencies.

Genetics laboratories should provide reports in an easily understandable form for referring physicians who are not genetics specialists. The evaluation of the quality of these reports should be an important component of the proficiency testing process. These reports, including interpretation of the results, should also be reviewed by the Health Care Financing Administration (HCFA) as part of

its inspection of laboratories performing genetic tests under CLIA88. The committee also recommends that laboratories performing genetic tests maintain a data base of qualified genetic counselors, genetic centers, and support groups (see Chapters 3, 4, and 6).

Genetic Tests for Rare Disorders

Genetic tests for rare disorders pose special problems in laboratory quality assurance because individual laboratories throughout the country are unlikely to perform enough of these tests to maintain proficiency. **Therefore, the committee recommends that tests for rare diseases be centralized in a few laboratories, to which specimens could be referred from other institutions.** The committee strongly urges the genetics community under the leadership of its professional societies to designate a small number of laboratories to serve as centralized facilities for rarely performed tests. An external proficiency testing program should be established for these central laboratories, and the genetics community should also study the possibility of setting a minimum volume for a specific genetic test that a laboratory must perform annually in order to obtain certification for that test and to ensure the quality of test performance. With its informatics and data base capabilities, the Special Information Services Program of the National Library of Medicine might also maintain a data base of centralized laboratories performing tests for rare disorders, as well as genetic counseling centers and support groups, which should be available to laboratories, providers, and consumers at no charge.

CLIA88

The committee recommends that most genetic tests be classified as "high complexity" under CLIA88, primarily to ensure the highest level of federal oversight of laboratories performing genetic tests. The committee recommends that HCFA create a new specialty of clinical genetics, incorporating the existing subspecialty of clinical cytogenetics, and the new subspecialties of biochemical genetics and molecular genetics as well. Maternal serum alpha-fetoprotein (MSAFP) testing and other methods of prenatal testing for birth defects should be incorporated into one of these three subspecialties. **The Centers for Disease Control and Prevention (CDC) should expand its proficiency testing programs for newborn screening.** HCFA should also give high priority to setting specific requirements for frequently performed prenatal tests and incorporating these standards in its training programs for current and new laboratory inspectors. All laboratories performing genetic screening, including state laboratories, should be required to participate in proficiency testing.

Laboratories using investigational devices for genetic tests (see below) are still covered under CLIA88 as long as test results are reported and used in clinical decision making and counseling, and these laboratories should also be subject to

external quality assessment. **Laboratories in academic health centers and elsewhere that conduct research, but that also perform genetic tests as a service (providing the results to referring laboratories or physicians, or directly to patients), fall under the purview of CLIA88 and should be subject to the same criteria, standards, and regulation as commercial genetic testing laboratories.**

Genetic Tests and the FDA

The committee is concerned that tests for newborns and other types of screening may be offered to the public before their safety, effectiveness, and clinical utility have been adequately assessed. **To remedy this, the manufacturer or user of a device for a new screening test (including state laboratories or health departments) should comply with the FDA's regulations for Investigational Device Exemptions (IDE).** For example, the investigational or "pilot" phase of screening should be conducted under a protocol approved by an institutional review board (IRB), and the pilot phase should be evaluated by an entity independent of the organization conducting the pilot study.

Compliance with FDA requirements is essential to ensuring safe and effective use of genetic tests, just as compliance with CLIA88 is essential for any laboratory performing genetic tests for clinical purposes. **All genetic tests should either be designated as investigational devices—subject to IRB approval and FDA regulation—or be submitted to the FDA for full premarket approval.** An Advisory Panel on Genetic Test Devices to the FDA should be established to ensure appropriate expert review for genetic testing products. Genetic diagnostic devices should be classified for full premarket approval by FDA (Class III), and the FDA should develop guidance to manufacturers for preparing premarket applications for genetic test devices (see Chapter 3).

DNA probes and other reagents that are essential to the performance of genetic tests are medical devices under current FDA law and regulation. **Consequently, whenever probes and reagents are used for clinical purposes, they must either be labeled "for investigational use only" (and must comply with FDA requirements for investigational use) or have FDA approval for marketing.** When genetic test devices are used investigationally for clinical purposes, manufacturers—including commercial or academically based laboratories preparing their own devices—should apply for FDA approval of an IDE, including an IRB-approved protocol and periodic reports on the results of their investigations.

Many institutional review boards lack experience in the review of investigational genetic testing protocols. The National Institutes of Health (NIH) Office for Protection from Research Risks has recently issued initial guidance for research involving genetics in its IRB *Guidebook*. **The NIH Office for Protection from Research Risks (OPRR) and the National Center for Human Genome Research (NCHGR) ELSI Program should continue to coordinate efforts to assist IRBs in coping with this responsibility.** Other federal agencies and pro-

professional groups should also consider developing guidelines to help IRBs cope with this added responsibility, such as the informed consent guidelines for research involving genetic testing developed by the Alliance of Genetic Support Groups and the American Society of Human Genetics (ASHG) (see Chapter 4).

The committee recognizes that, for very rare diseases and diseases with a long lead time between the time of the test and the appearance of disease, it will be difficult for FDA applicants to provide adequate data on safety and effectiveness for subjects of the type in whom the test would be applied (e.g., presymptomatic individuals). It may also be impossible to assess the sensitivity and specificity of prenatal tests by independent tests or histopathological examination of aborted fetuses. **For rare diseases, the FDA could grant the applicant "provisional premarket approval," a designation under which the test could be made more widely available while making the manufacturer responsible for obtaining additional postmarket data until sufficient data are available to warrant full "premarket" approval.** This process may require new legislation, but the committee believes that provisional premarket approval, with the sponsor responsible for periodic postmarket study, adequately covers the development of tests for rare conditions, which is the intent of the "humanitarian device exemption" (contained in the Safe Medical Device Amendments of 1990). And since manufacturers may be unwilling to go through premarket approval of tests for rare diseases, Congress should also consider the need for legislation in the spirit of the Orphan Drug Act that would give manufacturers an incentive to develop diagnostic medical devices for genetic tests of limited marketability.

GENETIC COUNSELING

Genetic counseling and education must be an integral part of genetic testing. Anyone who is offering (or referring for) genetic testing must provide (or refer for) appropriate genetic counseling and education prior to testing. To ensure that adequate genetic counseling is provided to all those seeking genetics services, a cadre of individuals trained in medical genetics and counseling must be available. Primary care practitioners and allied health professionals must have a minimal basic understanding of medical genetics and counseling (see Chapters 4 and 6). Efforts must also be made to ensure that the public is sufficiently educated to be informed consumers of genetics services (see Chapter 5).

Basic Tenets of Genetic Counseling

The committee believes that certain basic tenets apply, regardless of who is conducting the counseling and where it is being done. These include respect for the autonomy and privacy of the individual, the need for informed consent and confidentiality, and sensitivity to the counselor's tendency toward directiveness and paternalism (see Chapters 1, 4, and 8). The standard of care should be to

support the client in making voluntary informed decisions and to provide sensitive and empathic support for the emotional suffering caused by the genetic problem. **The goal of reducing the incidence of genetic conditions is not acceptable, since this aim is explicitly eugenic; professionals should not present any reproductive decisions as “correct” or advantageous for a person or society.** Research is needed to test alternative methods for providing genetic counseling (e.g., interactive video and computer methods with referral to a counselor for answers to questions), and to evaluate the costs and effectiveness of such changes.

One key to effective genetics services is the concept of the *teachable moment*, that is, the point(s) at which an individual, couple, or family, is best able to comprehend the information being given them. Unfortunately, the genetic counselor may not have the opportunity to counsel clients at more advantageous teachable moments—after some of the early shock and denial that often accompany genetic diagnosis have abated—because of restrictions on insurance reimbursement (see Chapter 7) and administrative impediments such as scheduling counseling on the day of testing. Studies are therefore needed on alternative approaches to genetic counseling, including the effects of differing levels of intensity of counseling and education both before testing—to help those at risk to decide whether or not they want to be tested—and after testing—to deal with the consequences of having the information (see below).

Physicians need to balance their desire to provide medical advice with respect for the patient’s right to make an informed decision that may be different from the one recommended by the physician. This is especially crucial in genetic testing, since genetic information carries more personal, family, and social risks and burdens than many other kinds of medical information. In particular, decisions about whether to reproduce or to abort an affected fetus are individual choices that should be left to each couple. Similarly, a decision about whether to test for the presence of genes or gene complexes that predict the likely development of future disease that cannot be treated should be an individual decision. And when treatment becomes possible, some of these decisions may still be painful, costly, and uncertain, and still require genetic counseling. **Nondirectiveness should always remain the standard of care for reproductive planning and decisions, and full informed consent before genetic testing will continue to be essential.**

Since genetics education and counseling are likely to be provided increasingly by primary care practitioners, these practitioners will need training to help them perform these functions appropriately and to know when to refer patients to specialized genetics personnel. Innovative educational devices to support genetics education and counseling should be designed and evaluated (e.g., video, interactive computer systems, and on-line data bases) in primary care settings. **Finally, the genetic counselor, as the messenger of potentially devastating or discriminatory information, must honor the patient’s desire for confidentiality except under rare special circumstances where breach of**

confidentiality is necessary to avert serious harm (discussed in Chapters 4 and 8). These special circumstances may involve the potential effects of genetic information on other family members or the potential harm to others if the information is not disclosed. Should a counselor anticipate a professional or personal need to disclose genetic information to a party other than the patient with whom he or she is consulting, then the potential for that disclosure should be addressed before any genetic testing services are rendered.

Tailoring Counseling to the Client

Research on the best ways to provide essential genetics education and counseling—by a variety of providers in a variety of settings—must precede efforts to streamline genetic counseling (see Chapters 6 and 9). The committee believes that understanding and recall of numerical risks of recurrence are too limited as measures of the success of or need for counseling. Beyond mere comprehension of numerical risk, genetic counseling is intended to assist individuals in evaluating the implications of genetic testing and genetic information, and in determining their own acceptable risk. **Since risk perceptions vary among individuals and among counselees and counselors, there is no one right way to present or interpret risk information; however, information must be balanced, and the process must be tailored to the client.**

Ethnic and cultural sensitivity is particularly important—genetic counseling should be tailored to the cultural perspective of the client, with special attention to differing cultures between client and health care professional. Research is needed to determine how best to provide genetic counseling in ways that are sensitive and appropriate to a variety of cultures and languages. Training in culturally appropriate language and delivery of genetic services should be included in the training of genetics and other health professionals who are likely to provide genetic testing and counseling in the future. It is also vital to destigmatize language describing genetic disorders and disabilities, and to present information about these conditions as fairly as possible. As one step in this process, genetic counseling and other genetics training programs should actively seek to increase the number of minority practitioners prepared to provide a variety of genetic counseling roles in a variety of settings (see Chapters 4 and 6).

PUBLIC EDUCATION

Much of the responsibility for preparing individuals to deal effectively with the ramifications of genetics must fall to the public education system. This includes both formal education, which takes place in the schools, and informal education, which takes place outside of school (see Chapter 5). Data from large-scale testing programs suggest that a clinic or a doctor's office is not the best context for a first exposure to genetic testing information, and that public education campaigns and counseling, generally, have a greater impact on individuals

with some previous exposure to genetic concepts. Decisions about genetic testing and its potential personal impact ultimately must be tied to preexisting knowledge and value systems; without such knowledge, individuals are more likely to make uninformed decisions or to cede all decisions about genetic testing to their health care professionals.

What do we want people to know, value, and do about genetic information? For example, people should know that DNA is the information molecule; they should value the variation and diversity that are expressed from that molecule, but they also need to appreciate the nature of the interaction among genes, the individual, and the environment. Perhaps the most important contribution of new knowledge about genetics is its ability to document a major biological basis for human variation. The old argument about nature versus nurture is outdated: as discussed throughout the report, both nature (biology) and nurture (environment) are important to health, and broad public understanding of the role of genetics (and its limits) is essential to avoid genetic reductionism and a "new eugenics."

Genetics education should also focus on concepts of genetic variability, diversity, and kinship. Such a focus will help to avoid simplistic explanations such as dichotomizing of genetic risks of complex diseases with genetic determinants as either categorically good news—that an individual has essentially zero risk for a particular disease—or categorically bad news—that he or she is virtually certain to develop it. Many disorders are of variable and often unpredictable severity, and much genetic risk assessment is of an inherently probabilistic nature. **Genetic testing is not an end in itself but rather a method for gaining information and insight to help people make personal and family health decisions.** The basic task is to educate the public so that each individual is capable of making an informed decision about seeking or using genetic testing and considering personal courses of action. In addition, the public and policy makers must be educated to help them develop appropriate public policy regarding genetic testing and screening. Genetic counseling will ultimately be made more effective by a better-educated public. This approach to public education about genetics will not be a simple or a small task.

The Human Genome Project's Ethical, Legal, and Social Implications Program should coordinate a public education initiative in genetics and expand its support for such efforts. Key policy and research strategies to be considered are (1) ensuring that appropriate educational messages about genetic tests and their implications reach the public; (2) incorporating principles, concepts, and skills training that support informed decision making about genetic testing into all levels of schooling—kindergarten through college; (3) enhancing consumers' knowledge and ability to make informed decisions in either seeking or accepting genetic tests; (4) establishing systems for designing, implementing, and maintaining community-based genetics education among population groups at higher risk of particular genetic disorders (e.g., increased risk related to race or ethnicity); and (5) enlisting the mass media to help decrease consumer confusion and in-

crease the knowledge and skills that will equip consumers to make the most appropriate decisions for themselves (see Chapter 5).

The National Science Foundation, the Department of Energy, the National Institutes of Health, and other organizations should expand their investment in public education related to the human genome. These efforts should (1) expand programs that support model educational initiatives for precollege science and undergraduate molecular biology; (2) collaborate with the Ethical, Legal, and Social Implications component of the Human Genome Project to encourage such programs to focus on the health, social, legal, and ethical issues raised by genetic testing and screening; and (3) require evaluation of educational interventions.

Broad public participation will be required to develop educational approaches that respect the widely varying personal and cultural perspectives on issues of genetics, and are tolerant and respectful of individuals with genetic disorders of all kinds. Particular effort will be needed to include the perspectives of women, minorities, and persons with disabilities, who may feel especially affected by developing genetic technologies. There is much to be learned from those who are particularly affected by genetic testing technologies, and from those affected by genetic disorders, including persons with disabilities and their families and support groups. The committee believes that genetics professionals and qualified educators must work with public representatives to identify the essential components of genetic literacy.

A "Consumer's Guide to Genetic Testing" should be developed (also see Chapters 1, 5, and 9) to provide information on genetic services, various genetic tests, and the implications of the tests so as to aid in providing balanced, reliable, readily understandable, and available sources of needed information. Innovative computer and interactive computer systems should also be developed to provide patients/clients with the latest information on genetic disorders and on genetic diagnosis, testing, and screening. If designed and used appropriately, such computer resources could assist genetics specialists and primary care practitioners by presenting patients with basic, self-paced genetics education and even presenting possible options for consideration of patients. The ELSI Program should therefore coordinate with the National Library of Medicine in developing innovative methods of providing information to the public similar to the on-line AIDS bibliography. More research is needed to determine which tasks in genetics education and counseling can be appropriately accomplished by using such techniques and to evaluate these techniques in various settings and populations.

PROFESSIONAL EDUCATION

The committee sees no prospect, in the foreseeable future, of having enough highly specialized genetics personnel to handle all genetic testing, including essential genetics education and genetic counseling. Therefore, policy discussion

should focus not only on training more genetic counselors and other genetic specialists, but on better educating the obstetrics, pediatrics, and family practice communities about the nature of genetic testing, diagnosis, and counseling.

Some progress has been made in increasing physicians' knowledge of genetic testing and their ability to take good family histories, particularly in specialties that involve more genetic tests (e.g., pediatrics and obstetrics; see Chapter 6). More recent graduates also know more than older physicians. Nevertheless, the committee is very concerned that relatively little progress has been made—certainly not enough to prepare physicians-in-training for the increasing requirements for genetic testing, education, and counseling projected for the future. **The committee strongly recommends that medical education begin to incorporate a genetic point of view throughout its curriculum, but especially in the critical clinical years, and that medical board examinations should include more questions on genetics.** More research is needed on knowledge of genetics and skills needed for genetics education and genetic counseling among all of these professional groups so that proper reforms can be implemented.

The biggest potential contribution of genetics to medical education may be its ability to document a major biological basis for human variation. Conventional teaching in medical school often disregards differences in etiology, presentation, response to therapy, personal preferences, and prognosis of people who may be “lumped” together under a single disease label. A true revolution will come much more from introducing a new way of learning about disease and health, of emphasizing the importance of individual differences, some but not all of which are genetically determined. Historically, the discovery of germs as causative agents in disease led to a reductionist germ theory that explained everything in terms of germs; the committee is concerned that the explosion of genetics knowledge may replace the reductionist germ theory with a *reductionist gene theory*—to the detriment of medical progress.

Genetics professionals and all others offering or referring for genetic testing should be trained in the ethical, legal, and social issues surrounding genetic diagnosis, testing, and screening. Laboratory personnel should be a special focus of such training about the complexities of genetic testing to adequately interpret tests, including a knowledge of test limitations and social issues surrounding genetic testing. **Of particular importance is training to deal with the sensitivities of genetics education and counseling, including the need for nondirectiveness, in counseling about reproductive options and about disorders for which no treatment exists.** Expanded undergraduate and graduate training of nurses in genetics, genetics education, and genetic counseling is also needed, along with the training of social workers in the special requirements of genetics education and counseling. With proper training, the integration of other health professionals such as nurses, nurse practitioners, social workers, psychologists, and primary care physicians, into the existing genetics services network will supplement the time and skills of traditional genetic counseling (see Chapter 4).

The accelerating developments of new knowledge in genetic testing will also require expanded formal continuing education programs in clinical genetics, including those geared to the genetic counselor, primary care practitioner, and social worker (see Chapter 5). The Ethical, Legal, and Social Implications Program should coordinate with professional genetics organizations and the National Library of Medicine to develop genetics education and dissemination programs for interested health professionals. Genetics specialists should develop and provide continuing education and training for other professionals, as well as take a leadership role in genetics education for the public. Other health care professionals should also participate in programs intended to increase public awareness and education about genetics.

More minorities should be recruited for training programs in all aspects of clinical genetics. This will be especially important in providing culturally sensitive and appropriate genetic testing, education, and counseling services in the future (see above), when so-called minority groups will comprise a majority of the population of the United States (see Chapters 4 and 6).

FINANCING OF GENETIC TESTING SERVICES

The cost and financing of genetic testing and counseling have had a profound effect on access to these services in the United States. No matter what aspect of genetics is discussed, it is almost impossible to keep the discussion from turning to issues related to financing, in particular the role of health insurance in genetic testing and counseling (see Chapter 7). The United States is the only developed country in the world without a social insurance or statutory system to cover basic expenses for medical services for most of its population. This creates problems of access and equity, especially for those low-income or high-risk individuals who are self-employed, work part-time, or are employed by small businesses and who may not be able to afford or obtain health insurance. Over 37 million people are without health insurance coverage in the United States.

Even for those who have health insurance, coverage for most preventive, screening, and counseling services may be excluded. These limitations of health care coverage in the United States particularly affect genetic services, which have an important counseling component. Insurance reimbursement or other financing of genetic testing is not generally available now in the United States. The committee also heard testimony that individuals whose insurance does cover some or all genetic services may be reluctant or unwilling to file claims for such services. They may fear that the genetic information they sought might be used to evaluate and deny their future applications for health or life insurance coverage, or lead to higher premiums or limited coverage. And, because so much coverage in the United States is employment based, people may also worry that their employer will have access to the information and use it (overtly or covertly) to discriminate against them (see Chapters 7 and 8).

In order to develop appropriate financing for genetic testing and counseling services, private and public health plans, and geneticists and consumers, should work together to develop guidelines for the reimbursement of genetic services. Such guidelines should address the issue of how each new genetic test should be assessed for its sensitivity and specificity in light of the availability of effective treatment, the consequences of the test, the evaluation of pilot study results, and when new tests are appropriate for use in routine clinical practice (see Chapters 1 and 7).

In addition, the insurance concept of what is considered *medically necessary* (and therefore reimbursable) should be expanded to include the *offering of appropriate genetic testing* and related education and counseling, making these genetic services reimbursable under health insurance plans. Medical appropriateness can often be established by a family history of the disorder. In pregnancy, medical necessity should be considered established for cytogenetic testing in pregnancies in women of advanced maternal age or considered at high risk based on other methods of assessing risk. The committee also recommends that newborn screening and MSAFP screening in pregnant women of any age be considered within the insurance definition of medically appropriate and be reimbursable under health insurance plans (see Chapter 7).

SOCIAL, LEGAL, AND ETHICAL ISSUES IN GENETIC TESTING

The committee recommends that vigorous protection be given to *autonomy, privacy, confidentiality, and equity*. These principles should be breached only in rare instances and only when the following conditions are met: (1) the action must be aimed at an important goal—such as the protection of others from serious harm—that outweighs the value of autonomy, privacy, confidentiality, or equity in the particular instance; (2) it must have a high probability of realizing that goal; (3) there must be no acceptable alternatives that can also realize the goal without breaching those principles; and (4) the degree of infringement of the principle must be the minimum necessary to realize the goal.

Voluntariness

Voluntariness should be the cornerstone of any genetic testing program. The committee found no justification for a state-sponsored *mandatory public health program involving genetic testing of adults or for unconsented-to genetic testing of patients in the clinical setting*. There is evidence that voluntary screening programs achieve a higher level of efficacy in screening, and there is no evidence that mandating newborn screening is necessary or sufficient to ensure that the vast majority of newborns are screened. *Mandatory offering* of newborn screening is appropriate for disorders with treatments of demonstrated efficacy

where very early intervention is essential to improve health outcomes (e.g., phenylketonuria and congenital hypothyroidism). One benefit of voluntariness and informing parents about newborn screening is that of quality assurance: parents can check to see if the sample was actually drawn. In addition, since people will be facing the possibility of undergoing many more genetic tests in their lifetimes, the disclosure of information to parents about newborn screening prior to the event can be an important tool for education about genetics.

Informed Consent

Obtaining informed consent should be the method of ensuring that genetic testing is voluntary. By *informed consent* the committee means a *process* of education and the opportunity to have questions answered—not merely the signing of a form. The patient or client should be given information about the risks, benefits, efficacy, and alternatives to the testing; information about the severity, potential variability, and treatability of the disorder being tested for; information about the subsequent decisions that will be likely if the test is positive (such as a decision about abortion); and information about any potential conflicts of interest of the person or institution offering the test (see Chapters 1, 3, and 8). **Research should therefore also be undertaken to determine what patients want to know in order to make a decision about whether or not to undergo a genetic test.** People often have less interest in the label for the disorder and its mechanisms of action than in how certainly the test predicts the disorder, what effects the disorder has on physical and mental functioning, and how intrusive, difficult, or effective any existing treatment protocol would be. Research is also necessary to determine the advantages and disadvantages of various means of conveying that information (e.g., through specialized genetic counselors, primary care providers, single disorder counselors, brochures, videos, audiotapes, computer programs).

Confidentiality

All forms of genetic information should be considered confidential and should not be disclosed without the individual's consent (except as required by state law, or in rare instances discussed in Chapters 4 and 8). This includes genetic information that is obtained through specific genetic testing of a person, as well as genetic information about that person that is obtained in other ways (e.g., physical examination, past treatment, or a relative's genetic status). The confidentiality of genetic information should be protected no matter who obtains or maintains that information. This includes genetic information collected or maintained by health care professionals, health care institutions, researchers, employers, insurance companies, laboratory personnel, and law enforcement officials. To the extent that current statutes do not ensure such confidentiality, they should be amended.

Codes of ethics for professionals providing genetic services should contain specific provisions to protect autonomy, privacy, and confidentiality. The committee endorses the 1991 National Society of Genetic Counselors (NSGC) statement of guiding principles on confidentiality of test results:

The NSGC support individual confidentiality regarding results of genetic testing. It is the right and responsibility of the individual to determine who shall have access to medical information, particularly results of testing for genetic conditions.

Confidentiality should be breached and relatives informed about genetic risks *only* when (1) attempts to elicit voluntary disclosure fail, (2) there is a high probability of irreversible harm that the disclosure will prevent, and (3) there is no other reasonable way to avert the harm. When disclosure is to be attempted over the patient's refusal, the burden should be on the person who wishes to disclose to justify to the patient, to an ethics committee, and perhaps in court that the disclosure was necessary and met the committee's test. Thus, the committee has determined that the disadvantages of informing relatives over the patient's refusal generally outweigh the advantages, except in the rare instances described above (see Chapters 4 and 8). **The committee recommends that health care providers not reveal genetic information about a patient's carrier status to the patient's spouse without the patient's permission, and that information on misattributed paternity should be given to the mother, but not be volunteered to her partner.**

As a matter of general principle, the committee believes strongly that **patients should disclose to relatives genetic information relevant to ensuring the health of those relatives.** Patients should be encouraged and aided in sharing appropriate genetic information with spouses and relatives. To facilitate the disclosure of relevant genetic information to family members, accurate and balanced materials should be developed to assist individuals in informing their families, and in providing access to further information, as well as access to testing if relatives should choose to be tested. Under those rare circumstances where unauthorized disclosure of genetic information is deemed warranted, the genetic counselor should first try to obtain the permission of the person to release the information.

The committee also endorses the principles on the protection of DNA data and DNA data banking developed in 1990 by the ASHG Ad Hoc Committee on Identification by DNA Analysis. In short, patients' consent should be obtained before their names are provided to a genetic disease registry, and their consent should also be obtained before information is redisclosed. **Each entity that receives or maintains genetic information or samples should have procedures in place to protect confidentiality.** Information or samples should be kept free of identifiers and instead use encoding to link the information or sample to the individual's name. Finally, any entity that releases genetic information about an

individual to someone other than that individual should ensure that the recipient of the genetic information has procedures in place to protect the confidentiality of the information.

Genetic Discrimination in Health Insurance

Legislation should be adopted to prevent medical risks, including genetic risks, from being taken into account in decisions on whether to issue or how to price health care insurance. Because health insurance differs significantly from other types of insurance in that it regulates access to health care—an important social good—risk-based health insurance should be eliminated. Access to health care should be available to every American without regard to the individual's present health status or condition; in particular, the committee recommends that insurability decisions not be based on genetic status (see Chapters 7 and 8).

Some of the committee's concerns about genetic discrimination in health insurance would be obviated by current proposals for national health insurance reform that would eliminate most, if not all, aspects of medical underwriting. **The committee recommends that insurance reform preclude the use of genetic information in establishing eligibility for health insurance.** As health insurance reform proposals are developed, those concerned with genetic disorders will need to assess whether they adequately protect genetic information and persons with genetic disorders from health insurance discrimination and discrimination in the provision of medical services (see Chapters 7 and 8).

Genetic Discrimination in Employment

Legislation should be adopted that forbids employers to collect genetic information on prospective or current employees unless it is clearly job related. Sometimes employers will have employees submit to medical exams to see if they are capable of performing particular job tasks. If an individual consents to the release of genetic information to an employer or potential employer, the releasing entity should not release specific information, but instead answer only yes or no regarding whether the individual was fit to perform the job at issue.

The committee urges the Equal Employment Opportunity Commission to recognize that the language of the Americans with Disabilities Act (ADA) provides protection for presymptomatic people with genetic risks for late-onset disorders, unaffected carriers of disorders that might affect their children, and individuals with genetic profiles indicating the possibility of increased risk of a multifactorial disorder. State legislatures should adopt laws to protect people from genetic discrimination in employment. In addition, ADA should be amended (and similar state statutes adopted) to limit the type of medical testing employers can request and to ensure that the medical information they can collect is job related.

RESEARCH AND POLICY AGENDA

In its efforts to complete a comprehensive overview of issues in genetic testing and screening, the Committee on Assessing Genetic Risks identified significant gaps in data, research, and policy analysis that impede informed policy making for the future. Surprisingly few data exist on the extent of genetic testing and screening today, for example, and no system is in place to gather data or to assess practices in relation to the committee's principles and recommendations for the future. The committee's review of the key data, research, and policy needs in genetic testing and screening has generated recommendations addressed to the Ethical, Legal, and Social Implications Program of the Human Genome Project, and several recommendations are addressed to other relevant agencies, including other components of the National Institutes of Health, the Agency for Health Care Policy and Research (AHCPR), the Centers for Disease Control and Prevention, the Food and Drug Administration, the Public Health Service (PHS), the Health Care Financing Administration, the Department of Health and Human Services (DHHS), the Department of Energy (DOE), the National Science Foundation (NSF), and a broad range of private organizations.

Policy Oversight

The committee strongly believes that effective oversight will be essential as genetic testing develops to ensure that genetic tests are validated and used appropriately, with respect for the potential harms such testing may pose. **For effective overall and continuing policy oversight, the majority of the committee recommends the creation of a broadly representative National Advisory Committee and Working Group on Genetic Testing to oversee professional practices and determine when new genetic tests are ready for wide-scale use in medical practice** (see Chapters 1 and 9).

Although the American Society of Human Genetics, National Society of Genetic Counselors, American Academy of Pediatrics, American College of Obstetricians and Gynecologists, and other professional organizations have developed policy statements on key policy issues in genetic testing, genetic testing has moved beyond the domain of genetics specialists alone. There is also a need for broad public involvement in the development of public policy concerning genetic testing and screening. As discussed throughout this report, genetic testing has broad health and social implications of both immediate and future concern to individuals and families with genetic disorders, genetic support groups, and the public at large. Increased public education will be required to equip the public to make informed personal and policy decisions in genetic testing (see Chapter 5). The proposed National Advisory Committee on Genetic Testing and its Working Group are intended to provide the essential broadly based scientific and public oversight for genetic testing and screening.

The committee also sees a need for broadly representative advisory bodies at the state level (see Chapters 1 and 9). These advisory bodies should be guided by the principles outlined in this report. They should guide state health departments and legislatures on such issues as when tests should be added to state-run screening programs and how to ensure that the offering, testing, and associated education and counseling are conducted in accord with the principles outlined in this report. **State statutes affecting genetic testing should not be unduly prescriptive or restrictive, and should provide latitude to such advisory bodies to modify state-run genetic testing programs.**

Research Policy

Much of current genetic testing grew out of the context of research studies, and some genetic testing is still being done in research settings. Research initiatives involving genetic testing are being supported and developed not only within the Human Genome Project, but also within the research programs of various components of the National Institutes of Health (including the National Institute of General Medical Sciences, National Cancer Institute, National Heart, Lung, and Blood Institute, National Institute of Child Health and Human Development, National Institute of Diabetes and Digestive and Kidney Diseases) and the Human Genome Program of the Department of Energy. **In developing and approving research protocols, the committee recommends that the NIH and the DOE consider the recommendations of this committee within the context of their research programs, including study of the psychosocial issues and implications of genetic testing and the potential for harm from the use and misuse of genetic information.** This is especially significant where there is no treatment available for the disorders, as will often be the case in the near future. In developing requests for proposals and requests for applications and in reviewing research, demonstration projects, pilot studies, clinical trials, and family studies in genetics, funding agencies should pay particular attention to psychosocial issues and should assess the availability of appropriate genetic counseling and follow-up services as elements of study design.

Need for Additional Standards

The committee identified several areas for which additional standards were needed concerning who should be tested, for what disorders, and at what age. **While existing standards may have been adequate for the past, new standards must be developed in response to rapid developments in genetic testing methods that are now experimental. In particular, additional standards are needed for prenatal diagnosis, predispositional testing, and multiplex testing** (see Chapter 9). Research and policy analysis is needed in prenatal genetic diagnosis to address problems such as the complexities of identifying fetal cells in maternal blood, maternal serum alpha-fetoprotein screening, notions of "perfect-

ibility,” use of prenatal diagnosis and selective abortion to choose the sex of the fetus, the special impact of prenatal diagnosis on women, and carrier detection in pregnancy rather than prior to conception (see Chapters 2 and 9). Reproductive genetic decisions raise some of the most deeply personal and troubling issues in genetic testing. Professional groups need to work together and develop innovative methods for involving the public in the development of standards for the use of these technologies (see Chapters 2, 3, 4, and 9).

Standards are also needed for genetic testing for predisposition to late-onset disorders. There is an important “window of opportunity” for considering these issues now, before predispositional genetic testing becomes widespread. Tests for predisposition to common disorders will be of great commercial interest, and could have substantial potential for harm to individuals and families in terms of insurability and employability, as well as substantial benefit from the potential of early preventive and therapeutic interventions. Strict guidelines for efficacy will be necessary to prevent premature introduction of this technology (see Chapters 1, 2, and 9). **The committee believes that population screening for late-onset diseases should be considered only for treatable or preventable conditions of relatively high frequency and only after appropriate, reliable, sensitive, and specific tests become available; and such tests should be voluntary.** In general, because of the significant medical and psychosocial consequences of predictive testing, the committee believes that testing of minors should be discouraged. Instead, **research should be undertaken to determine the appropriate age for testing and screening for genetic disorders in minors in order to maximize the benefits of therapeutic intervention.**

Multiplex testing—multiple genetic tests on a single blood or other tissue sample—represents one of the most likely innovations in genetic testing. **Consequently, the committee also recommends the development of standards for multiplex genetic testing.** Innovative methods are needed to group tests by related types of disorders that raise similar issues (including the availability of effective treatment and how soon treatment needs to be instituted), as a basis for appropriate education, informed consent, and genetic counseling. This will allow potential screenees (or parents) to choose which, if any, group of tests they feel is appropriate for them. Tests for untreatable disorders should not be multiplexed with tests for disorders that can be cured or prevented by treatment or by avoidance of particular environmental stimuli. Multiplex testing is also an area in which more research is needed to develop ways to ensure that patient autonomy is recognized (see Chapters 1, 2, 3, 4, and 8).

Policy Research Needs

The committee identified significant data and policy research needs related to genetic testing (see Chapter 9). In addition to its other recommendations, the committee identified several areas in which policy research is needed, including

- pilot studies of new tests before wide-scale introduction;
- cost-effectiveness analysis of genetic testing;
- critical deficiencies in data on genetic services;
- research on population distribution and heterogeneity of traits involved in genetic or genetically influenced disease; and
- assessment of what has been learned thus far from ELSI research and policy studies.

Dr. HOLTZMAN. These are only a few of the extramural activities supported by the ELSI Program. The NIH, DOE, ELSI working group has already issued a report, and again, you have heard about this from its Task Force on Insurance and Genetic Testing, including recommendations on genetic testing and insurance.

The Working Group has recently initiated a Task Force on genetic testing whose purpose is to assure that policies are in place to promote the safe and effective use of genetic tests. Genetic discrimination by employers and privacy issues are other areas in which the working group has been active.

Thus the problems are being tackled, in no small part due to the wisdom of the Congress in assuring the availability of funds to study these and other issues related to the ethical, social, and legal implications of the human genome project.

We are off to an unprecedented start in anticipating the potential harmful effects of a powerful new technology, rather than waiting until they become ingrained in our health care.

Thank you again for the opportunity to speak.

[The prepared statement of Dr. Holtzman follows:]

TESTIMONY OF NEIL A. HOLTZMAN, M.D., M.P.H.
 BEFORE THE SUBCOMMITTEE ON ENERGY,
 COMMITTEE ON SCIENCE, SPACE, AND TECHNOLOGY
 U.S. HOUSE OF REPRESENTATIVES
 OCTOBER 4, 1994

Chairperson Lloyd, Members of the Committee, Ladies and Gentlemen:

Thank you for giving me the opportunity to discuss some of the implications for society of technological breakthroughs in human genome research. My remarks will focus on new genetic tests made possible by the identification of genes that play a role in human diseases. By way of background, I am a pediatrician and geneticist, and Professor of Pediatrics, Health Policy, and Epidemiology at The Johns Hopkins Medical Institutions. I am a member of the Joint Working Group on Ethical, Legal and Social Implications (ELSI) of Human Genome Research of the National Institutes of Health (NIH) and Department of Energy (DOE). I am also a recipient of grants from the ELSI program of the National Center for Human Genome Research, NIH. Much of my research has been at the interface of basic science and medical practice, attempting to understand the role of genes in disease and how breakthroughs in genetics reach the public in the form of tests for genetic disorders.

The discovery of a disease-related gene depends on finding variant forms of the gene--alleles--in people with the disease that are absent in people without the disease. Using recombinant DNA technology, this approach has yielded genes for cystic fibrosis, Huntington disease, muscular dystrophy, neurofibromatosis, fragile X, familial forms of colon cancer, melanoma and, very recently, breast cancer, to name but a few. Once these disease alleles are identified, it is technically trivial to devise probes that can be used in clinical settings for detecting healthy individuals who are going to get the disease. Whether the tests can attain this goal safely and effectively is not, however, a trivial matter.

Let me explain why. The initial discovery of a disease-related gene is made in a few families. But will the alleles that are associated with disease in these families be the same ones as in others with the disease? Let me give two examples that illustrate problems.

Cystic fibrosis The alleles that proved the identify of the cystic fibrosis (CF) gene accounted for fewer than half of all patients with CF (but all of the patients within the families under investigation). To have begun clinical testing with just these probes would have missed over half the cases. (Since the discovery of the CF gene, scientists have found over 300 different alleles that can lead to cystic fibrosis. Today, we can detect, among white populations, about 90 % of carriers of cystic fibrosis alleles. In non-white populations, in which the disease occurs less frequently, the percentage is considerably lower.)

Breast cancer Current estimates are that only about 10 % of all people who will get colon or breast cancer have alleles that greatly increase their risk. People who test negative may assume, erroneously, their risk is low and fail to take other steps to detect disease early. Negative genetic test results could lull them and their physicians into neglecting the disease as a possible cause when symptoms do appear. (A person from a high risk family with a negative test has an appreciably lower risk than before testing and could be spared interventions recommended for those who test positive. Both could be spared the anxiety of uncertainty.)

The chance of missing people who carry alleles for disease -- scientists call this the sensitivity of a test -- is not the only error intrinsic to genetic tests. People with positive test results will not always develop the disease or have a high risk of having children with the disease. Scientists call this the predictive value of a positive test. In high risk families, in which several relatives have colon or breast cancer, people found by testing to have a susceptibility-conferring allele will not always get the disease even if they live past 80. Cancer is a complex disease in which certain alleles increase susceptibility, but other genetic as well as dietary and environmental factors must be present before malignant lesions appear. Our understanding of these factors is rudimentary. A woman who is told she has an allele for breast cancer may decide to have a prophylactic mastectomy but she may never develop breast cancer. (This is unlikely in families in which several close relatives (sisters or mother) have already developed cancer, but we remain ignorant of whether finding the allele in people without a family history carries the same risk.) The role of genes in other common disorders, such as coronary artery disease and mental illness, is also exceedingly complex.

For single-gene (Mendelian) genetic diseases, a positive result for being a carrier of a recessive or X-linked disorder seldom carries any risk to the individual. For recessive disorders, the chance that a carrier will have children with the disorder depends on his or her partner also being a carrier. People are not always told, and may not understand, that a positive test result does not mean that disease will occur in them or in their children. Deficiencies in communication and/or understanding have been documented in carrier screening for sickle cell anemia, Tay Sachs disease, and cystic fibrosis.

Even when positive test results carry a high probability that disease will appear, individuals may not necessarily benefit from the knowledge. First of all, there may be little of proven efficacy that can be done. Fran Visco, the President of The National Breast Cancer Coalition, a consumer organization, pointed out last month that a positive genetic test for familial breast cancer gives a woman information about her risk of getting a disease for which there is no known cure and which she cannot prevent. Second, people with positive test results risk losing their health insurance as long as insurers can deny coverage, or charge higher premiums, to those with pre-existing conditions, of which inheriting a disease allele is one. Visco goes on to say that a genetic test for breast cancer may actually do harm because women who test positive risk losing their health and life insurance. Third, genetic tests, which are not explicitly included under the Americans with Disabilities Act, could be used to deny jobs even when a positive test result does not impair the worker's ability to perform the job. Employers are also able to exclude conditions for which employees have positive genetic test results from their health benefits. Fourth, genetic test results could be communicated to relatives or others without the knowledge and permission of the person being tested, who might be harmed as a result.

After a disease gene has been identified much needs to be done, therefore, before that discovery can be translated into effective genetic testing whose benefits outweigh the risks. Despite lack of data on test sensitivity and predictive value, on adverse reactions to testing, or on the efficacy of follow-up interventions, medical-centers and commercial clinical laboratories are offering genetic tests for colon and breast cancer and Alzheimer disease, to name the more common disorders. They can do this because the Food and Drug Administration (FDA), which could require the collection of such data if the test or its components were being sold to other users, has little authority to regulate laboratories who provide these tests as services. The FDA could, however, require these laboratories to participate in protocols to assess the essential components of genetic testing, most of which

have not been approved for clinical use. Unfortunately, the agency does not have the resources to do so.

Nor is there much assurance, in most states, that the laboratories offering these tests are sufficiently proficient. People are sometimes given wrong information because of avoidable mistakes in the laboratory. Although the Clinical Laboratories Improvement Amendments of 1988 provides a framework for assuring the quality of laboratories performing genetic tests, the Health Care Financing Administration, which administers the Act, has not yet applied its provisions to the specialty of genetic testing.

The decision of a person to have a genetic test is not an easy one. With doubts about the efficacy of interventions to prevent cancer or Alzheimer disease, for instance, some people would prefer not to know that they are susceptible. Some might fear losing their health insurance if they tested positive. Carrier testing and prenatal genetic diagnosis present people with options for avoiding the conception or birth of children with serious genetic disorders. Some people will reject all of these options and would, therefore, prefer not to be tested. Geneticists and genetic counselors, who have been trained to present the options in a non-directive manner, are in short supply. Their numbers are unlikely to increase substantially. Consequently, non-geneticist physicians, especially primary care physicians, will increasingly provide information to patients about genetic testing. In work supported by the ELSI Program of the National Center for Human Genome Research, NIH, my colleagues and I have shown that primary care physicians have significant gaps in their knowledge of genetics and genetic testing. Many of them believe it is appropriate to recommend a course of action to their patients in deciding to have a prenatal diagnostic test. With your permission, I would like to enter the published reports of two of our studies into the record.

Work of the type I have just described, supported by the Human Genome Project, is helping this society to chart a safer course in the pathway from discovery of genes to routine use of genetic tests. The National Center for Human Genome Research, in cooperation with other Institutes at NIH, has provided support to several medical-centers to establish pilot programs for cystic fibrosis carrier screening and to others to explore issues in testing for hereditary breast, ovarian, and colon cancer. NIH and DOE also supported the convocation of an Institute of Medicine Committee to consider ethical, legal and social implications of genetic testing. With your permission, I would like to enter the executive summary of the Committee's report into the record. These are only a few of the extramural activities supported by the ELSI Program. The NIH/DOE Working Group has already issued a report of its Task Force on Insurance and Genetic Testing, including recommendations on genetic testing in insurance. The Working Group has recently initiated a Task Force on genetic testing whose purpose is to assure that policies are in place to promote the safe and effective use of genetic testing. Genetic discrimination by employers and privacy issues are other areas in which the Working Group has been active.

Thus the problems are beginning to be tackled, in no small part due to the wisdom of the Congress in assuring the availability of funds to study these and other issues related to the ethical, social, and legal implications of the Human Genome Project. We are off to an unprecedented start in anticipating the potential harmful effects of a powerful new technology rather than waiting until they become ingrained in our health care.

Thank you again for the opportunity to address you.

Mrs. LLOYD. Thank you very much, Dr. Holtzman. My colleagues have gone for a recorded vote and I choose to remain with you all and not make a recorded vote.

Dr. Clayton.

Dr. CLAYTON. Madam Chair, Members of the committee, I would like to thank you as well for inviting me to address you about some of the ethical, legal, and social issues posed by genetics.

In the next few minutes, I propose respectfully to disagree with Dr. Patrinos and sort of spell out for you in a little bit more detail some of the many reasons why people may have to be legitimately concerned about genetic information and that there are many sources from which genetic information can be obtained over which people have little control.

My own background in these issues are that I am a primary care physician, one of the—and I am a—have also been a recipient of funding from the NIH to study some of these issues, and I also have written extensively about the law's approach to the—

Mrs. LLOYD. You are an extremely qualified woman, and we are very delighted to have you with us today. I was looking at your biographical sketch. I was very impressed.

Dr. CLAYTON. I will conclude that there is a strong need to construct stronger mechanisms to protect the confidentiality of genetic information and ultimately a need for health care reform, I think, of which we already know, but which the advances in genetics make abundantly clear.

We do know that genetic information can be highly useful to people. It can enable them to prepare for and even avert some risk to their own health and the health of their loved ones. We do know, for example, that if treated, children with metabolic diseases like phenylketonuria and galactosemia can lead almost normal lives, whereas without treatment, they would be profoundly retarded or even die.

But we also know that there is much genetic information that we are less clear about what to do. As Dr. King has already made abundantly clear, we don't know exactly what it means to be found to have a mutant allele for BRCA1.

And as Dr. Holtzman has already made clear, people can also use genetic information to make reproductive choices that are more in line with their own goals. But, as we also know, learning about one's genetic makeup is not without cost. Even when the implications are properly understood, people may be made uncomfortable or anxious by having more knowledge about the risks of the disease that they or their families may face. Women in particular may be anguished by the implications of prenatal diagnosis, and these implications can be heightened by the fact that many of the people who receive this information may be clinically well, may receive—may be receiving this information at a time in their life when they perceive of themselves as not ill.

It has also been made abundantly clear that most genetic information is probabilistic rather than certain. The fact that a person has a gene for colon cancer means that he is more likely to get colon cancer, but no one knows when or if he in fact will. Probabilistic information is not something people in general do very well with.

And then as Dr. Holtzman has also made clear, the fact of the matter is, physicians and patients can simply misunderstand what the implications of genetic information are.

Another thing that particularly has been revealed in some of the work that has been funded by the ELSI program is that getting genetic information can have a profound impact on relationships within families, some of which may be less than obvious at the outset.

In a study of families at risk for cystic fibrosis, for example, Joanna Fanos demonstrated that some families simply are silent about the disease, refusing to share information about inheritability with some family members who are at risk. In some families it appears that this silence is a result of shame or denial, but in other families, it is a result of a desire by the person with the information to protect their relatives from anxiety or even from losing their insurance, a subject to which I will return in just a minute. And even if information is shared within families, that can have effects as well.

We all know that family members not infrequently put pressure on each other to have tests, to share information, and do other things like that. But we also know that, at least under our current legal system, family members do not have a right to get medical or genetic information about each other without the consent of the person about who the—about whom the information obtains. In our society, genetic information is personal and private in the family setting.

And if the information is shared, family relationships can be altered in other ways as well. Sometimes a family member who is found not to be a carrier of the particular gene that runs in the family may find themselves ostracized from the family because they are no longer under the family cloud. The person who is found to have the gene may perhaps happily be included within the family fold.

Now, pointing out these implications, both for the person's view of themselves and for the implications for their family is not to say that we shouldn't be sharing this information. I think that that course would be far too paternalistic, but rather it is to say that when people make decisions about having genetic testing, they need to be apprised about what the potential consequences to them might be so that they can make better decisions that fit more with their own lives.

Now, it is the case that when we as physicians offer tests to patients or any other thing, we are supposed to tell them what the possible implications are going to be. However, we need to be doing considerably better in this regard.

But the thing that bothers people, I think, more than anything else is not so much what the impact on their own self-image is or the impact on their family relationships, but rather the one to which Dr. Holtzman has already alluded, namely the impact on insurability.

We too are recipients of one of the grants to look at the dispersion of carrier testing for cystic fibrosis in the general population, and we have just completed a survey where we asked people why they didn't do it, and what we found was the factor that was men-

tioned most often was fear of losing insurance, even though, as we asked these people to fill out these questionnaires, we told them that if they were found to be carriers, they would not be at risk of getting cystic fibrosis themselves and that there was only a risk that their children would be affected.

Even so, more than any other—more than concerns about abortion, more than concerns about their partner's opinion, more than concerns about anything else, the number one thing that was most important to them was concerns about insurance.

Now, you can say that their fears are unfounded. We as yet have only a little evidence that people who have reproductive risks are having trouble getting health insurance for themselves and their families, but whether those fears are founded or not, people are very worried about the effect of getting information on their insurability, and these concerns affect their willingness to have genetic tests. Those for whom genetic tests can provide information about their own future health have much more reason for concern about insurance as we have already heard.

A woman who learns that she carries 2 mutant gene for BRCA1 would almost surely be unable to get life insurance or health insurance in the private market. We already know that some people are choosing to pay cash when they get genetic testing because they don't want their insurer to find out about it. Unfortunately, paying cash doesn't avoid all the problems.

One problem it doesn't avoid is that the insurer can always ask you: "Have you had a genetic test?" And then the patient is put to the question of whether they are going to lie or whether they are going to go ahead and tell the truth. And that's a fundamental problem. Even beyond that, people may feel uncomfortable or even be harmed if they have information about their own genetic risks that they are unwilling to share with their—with their physician or other health care provider because they are desperately afraid that that information is going to get in their medical records.

And then finally, as Dr. Holtzman has also made clear, concerns about insurability affect decisions about employment. An article in *The York Times* a few years ago made clear that about 20 percent of Americans currently perceive that they have job lock secondary to concerns about insurance and it really is unclear how much Americans are protected from discrimination by their employers by the Americans with Disabilities Act. At the moment, it is pretty clear that the protection is incomplete.

Now, so far I've focused on the reasons why people may want to ensure the privacy of their genetic information and the factors that they may want to think about when they are making decisions about having genetic tests.

The second point that I want to make is this, namely, that ordinarily people think they have control over what tests are done about them. And the fact is that there are tissue samples in storage for millions of Americans which could be used for genetic testing. Every—virtually every time a baby is born in the United States, blood tests are run to see if the baby has PKU or galactosemia so that treatment can be started early.

For the most part, these tests are a really good idea. But it's the case that some States have held onto these blood samples for over

20 years. It's also the case that when one has surgery, pathologists are required to hold onto the tissue that's obtained at surgery. And, again, some States require that pathologists hold onto these tissues for 20 years.

Now, the good news is that so far use of these sorts of samples for clinical tests that are relevant—that are relevant to the individual are not currently done, being done without consent. But there is no technical reason why a tissue sample that's in a pathologist's bank couldn't be used for genetic tests without asking the person.

And so I think as we—this possibility is something that is currently being considered and we are currently in the process of developing guidelines to make clear that consent needs to be obtained. But at the moment, I think it's important to realize that there is a lot of genetic—potentially available genetic information out there.

In conclusion, in the last few years, as the result of analysis and research, much of it funded by the ELSI programs of the DOE and NIH, we've learned much more about how genetic information affects people, how it affects themselves, their relationships with their families, their access to insurance and their interactions with their employers. And we are clear that people need to know about these consequences before they decide about testing. And if they are to make informed decisions, they need to know reliably who is going to have access to this information and who is not.

I would contend that our current protections for confidentiality are inadequate to the task, particularly as we move toward the creation of more extensive collections of health information and as we realize that tissues from which genetic information can be obtained are widely available.

And finally, the impact of concerns about access of insurance on people's decisions about genetic testing strengthens—strengthens the case for health care reform to ensure access to adequate health care for all Americans without exclusions for preexisting causes.

Thank you very much.

[The prepared statement of Dr. Clayton follows:]

TESTIMONY BEFORE THE SUBCOMMITTEE ON ENERGY
 COMMITTEE ON SCIENCE, SPACE, AND TECHNOLOGY
 U.S. HOUSE OF REPRESENTATIVES
 Ellen Wright Clayton, MD, JD
 October 4, 1994

Thank you for inviting me to address you about some of the ethical, legal, and social issues posed by genetics. In the next few minutes, I hope to demonstrate that people have many reasons to be legitimately concerned about genetic information and that there are many sources from which such information could be obtained over which individuals have little control. I will conclude that there is a strong need to construct stronger mechanisms to protect the confidentiality of genetic information and ultimately a need for health reform.

Genetic information can be highly useful to individuals. It can enable them to prepare for and even avert some risks to their own health and the health of their loved ones. We know, for example, that if treated, children who have galactosemia or phenylketonuria (PKU) can lead almost completely normal lives. Without treatment, these children would be profoundly retarded and could even die. Some people may also use genetic information to make reproductive decisions that more closely fit with their own goals.

Learning more about one's genetic makeup is not without cost. Even when the implications are properly understood, people may be made uncomfortable or anxious by having more knowledge about the risks of disease they or their family may face. Women, in particular, may be anguished by the implications of prenatal diagnosis. This anxiety may be heightened by the fact that oftentimes the person who receives it is clinically well. In addition, most genetic information is probabilistic rather than certain -- the fact that a person has a gene for colon cancer means that he is more likely to get cancer but no one knows when or even if he actually will. In addition, people and their physicians may simply misunderstand the implications of genetic information.

Having more specific genetic information can also change relationships within families, sometimes in ways that initially may seem unexpected. In a study of families at risk for cystic fibrosis, for example, Joanna Panos demonstrated that some families simply are silent, refusing to share information about heritability with family members who are at risk. This silence is sometimes the result of shame or denial. Silence may also

result from a desire to protect relatives from worry or from losing their insurance. Sharing the possibility of genetic risk can disturb family relationships as well. People may feel entitled to pressure their relatives to have tests or to learn more about their relatives' genetic test results. But the fact is that family members cannot use the law to force each other to be tested or to reveal their results and physicians generally cannot reveal this sort of information without the person's consent. Genetic information is personal and private in the family setting. If test results are shared, relatives who are found not to be at risk for passing the disease on to their children may find themselves ostracized because they are no longer under the "family cloud." Perhaps happily, those who have the gene may be included more fully into the family fold. Thus, how genetic information is viewed within families can be a source of conflict and concern. The message here is not that people should be denied genetic testing to protect them from interpersonal psychosocial difficulties. That sort of paternalism is not warranted, especially since many people and families find this sort of information to be helpful. People do, however, need to be told about the possible personal and family consequences so that they can think about what the information may mean for them before they decide whether or not to accept testing.

People appear to be most concerned, however, about the revelation of genetic information to third parties, such as their employers and insurers. We interviewed more than 300 people about their views about carrier testing. People who are carriers for many genetic diseases will never be affected themselves, but their children have a greater chance of having that particular inherited disease. More than four out of five people said that when they were deciding about whether to have carrier testing, the risk of losing their insurance was important or very important. In fact, fears about insurance were the most important of the ones that we asked about. In the group we asked, more than a third felt that the risk of losing one's insurance if one was found to be a carrier was medium or high.

One could argue that these people's fears are unfounded. We have only a little evidence that people who have a risk of having children affected with genetic diseases are having trouble getting health insurance for themselves and their families. But whether founded or not, people are worried about the effect of getting information regarding reproductive risks on their insurability. These concerns affect their willingness to have genetic tests.

Those for whom genetic tests can provide information about their own future health have more reason for concern about insurance. A woman who learns that she carries the gene for BRCA1 would almost surely be unable to obtain health or even life insurance in the private market. We already know that some people are paying cash for genetic tests in an effort to keep

their insurer from finding out that the tests were performed. Unfortunately, paying cash may not avoid all the problems. Insurers can still ask people whether they have had tests, and people will need to decide how they will answer. People may also feel uncomfortable and may even be harmed if they have information that may be relevant to their health care that they dare not share with their physician for fear that the information will end up in their medical record.

Concerns about insurance can also affect people's decisions about their employment. We already know that many people already experience "job lock" because of their fears about insurance. It is unclear how much employers can use genetic information to decrease the costs of providing health care for their employees. The Americans with Disabilities Act is a help, but it does not provide complete protection to employees when they or their families are known to be at risk for genetic disorders.

So far I have focused on the reasons why people may want to ensure the privacy of their genetic information and the factors they may want to consider in deciding whether or not to undergo genetic testing. The second point I want to make is this. We ordinarily think that people have control over what tests are done to learn more about them. The fact is that tissue samples have been stored for millions of Americans which could be used for genetic testing. Every time a baby is born in this country, samples of blood are taken for testing for certain diseases that need to be diagnosed early if the affected child is to do well. For the most part, these programs are a good thing. But some states hold onto these samples for years. Whenever a person has some tissue removed at surgery, the hospital's pathology lab is required to retain some of the tissue, in some states for as long as twenty years. Here as well, retaining tissue samples can be useful for the person's later clinical care. These samples represent a powerful repository of genetic information. At present, genetic testing for clinical purposes is not being performed on such samples without the person's consent. Such testing is technically possible without further involvement by the individual, however, and if undertaken, genetic information about that person could become available. The risk that unexpected or unwanted genetic information would be revealed is small, but if it were to occur, the information could upset the person, affect their interpersonal relationships, or cause them to lose their insurance.

In conclusion, in the last few years as a result of analysis and research, we have learned much more about how genetic information affects people -- personally, within their families, with their employers, and with their insurers. People need to know about these consequences before they decide about testing. If they are to make informed decisions, people need to know reliably who will have access to this information. Our current mechanisms for the protection of confidentiality are inadequate to the task, particularly as we move toward creation of more

extensive collections of health information and as we realize that tissues from which genetic information can be obtained are widely available. And finally, the impact of concerns about access to insurance on people's decisions about genetic testing strengthens the case for health care reform to ensure access to adequate health care for all Americans.

Mrs. LLOYD. Thank you very much, Dr. Clayton.

Dr. Nishimi, we look forward to hearing from you now.

Dr. NISHIMI. Madam Chairman, it is a pleasure to appear before you today. Before beginning my testimony, I would like to thank you for myself and on behalf of OTA for the support that you have given OTA over the years. We are all very sad down at 600 Pennsylvania Avenue to see such a good friend of the agency leave and we wish you well.

Mrs. LLOYD. Thank you very much.

Dr. NISHIMI. Madam Chairman, as you are aware, medical technology now includes genetic tools that can deliver predictive information with increasing accuracy. The ever-expanding array of genetic tests raises important questions for individuals and societies.

My written testimony focuses on an overview of six issues that OTA has identified in its reports as being important for Congress to consider: First, the extent to which the United States will need additional genetic specialists as well as the need for all health care providers to have increased and continuing education in genetics; second, quality assurance and government oversight of laboratories that perform tests and the companies that develop test kits; third, the privacy considerations of DNA databases in genetic research; fourth, reproductive issues, including the issue of prenatal testing and abortion, as well as genetic basic research such as preimplantation and genetic diagnosis and embryo research; fifth, the issue of discrimination of people with genetic illnesses or those who have predispositions to genetic disorders or are carriers for conditions the new tests can detect; and sixth, genetics education for the public.

In the interest of time, what I'd like to do is not delve into these matters further but, rather, focus on the possible policy mechanisms to address these and other ethical, legal, and social issues that the human genome project raises.

Before doing that, however, I would like to mention one additional issue that has been mentioned here today, but to emphasize that this issue nearly engulfs any discussions about genetic tests. I'm referring, of course, to the issue of access to health care and health insurance reform. Suffice to say that access to genetic tests and the services related to them are inextricably linked to the broad issue of health care reform in the United States.

Turning now to the policy mechanisms. Since fiscal year 1988 when the Federal Government first committed to funding the human genome project, concern has been raised about the mechanisms by which the ethical, legal and social issues the project raises would be identified and explored and then appropriate remedies reviewed and implemented. To address such considerations, the National Institutes of Health and the Department of Energy each funds an ethical, legal, and social issues program through a set-aside of 3 percent to 5 percent of annual appropriations for the project.

The ELSI programs operate independently in the model of peer review competition for research grant funding. The ELSI working group, which is a joint NIH-DOE effort, advises both programs. And, initially, the working group framed the agenda and established priority research areas. The nature of grant programs, how-

ever, means the ultimate direction evolves from the bottom up; that is, from the individual perspectives of researchers pursuing independent investigations rather than from the top down; that is, through policymakers or an overarching Federal body.

No formal mechanism exists for ELSI funded research findings to directly make their way back into the policy process. Despite the recommendations of at least two successive Congresses that a commission-like mechanism be adopted to examine and implement policy guidelines derived from the ELSI grants, no such entity has materialized. In the past few months, however, NIH has moved to expand its policy analysis capacity and so the current extent to which their policy implementation moves forward is in flux.

Regardless of the approach and the structure that NIH, DOE, and the ELSI working group ultimately adopt, at least one other mechanism is under development that could provide the opportunity to make policy recommendations related to genome research. As has been mentioned, on August 12 of this year, the White House, Office of Science and Technology Policy published a charter for a proposed National Bioethics Advisory Commission, which I will refer to as NBAC.

NBAC, if constituted, could provide a high profile cross-agency forum to address some issues pertinent to the human genome project. For example, the draft charter includes the direction that "as a first priority, the Commission will direct its attention to consideration of issues in the management and use of genetic information." Such a study is only one of two directly identified as NBAC topics. Moreover, NBAC recommendations may carry significant weight by virtue of the position of the Commission in the executive branch hierarchy.

Additionally, the draft charter contains language that requires departments and agencies to respond to any NBAC recommendations. The draft NBAC charter states that "the Commission may specifically identify the Federal department, agency, or other entity to which particular recommendations are directed and request a response from the Federal department, agency, or other entity within 180 days of publication of such recommendations." In other words, should an agency opt not to implement an NBAC recommendation, the agency must publish a notice that details the reasons it is not doing so.

In our report on bioethics, OTA found that such a forcing clause is an important factor in the past effectiveness of bioethics commissions. Still, it's important to keep in mind that NBAC has been designed to undertake work that is of interest to multiple agencies. Thus, some items important to policy analysis and the human genome project may be viewed as too narrow for NBAC to consider; hence, it will be important to examine the relationship between NBAC, the ELSI working group and NIH's intramural policy analysis capacity. Because none of the entities is currently in place, however, it is impossible for OTA to speculate any further about how this landscape will shape up.

Madam Chairman, in concluding, I note that what is important is striking a balance between our intellectual curiosity and pursuing an exciting line of inquiry against our obligation to see that applications of any information gained are ethical and legal.

No one can estimate in common terms what it means to an individual to possess information about his or her genetic status. As our knowledge of the human genome increases, what we do with genetic information will depend on the perceptions, beliefs and values of all Americans. Public understanding of this new knowledge and its implications is necessary for its wise and thoughtful application.

I'll be happy to answer any questions.

[The prepared statement of Dr. Nishimi follows:]

OTA TESTIMONY

Statement of

ROBYN Y. NISHIMI, Ph.D.
Senior Associate
Office of Technology Assessment

Before the

Subcommittee on Energy
Committee on Science, Space and Technology

U.S. House of Representatives

October 4, 1994

***THE HUMAN GENOME PROJECT: ETHICAL, LEGAL, AND SOCIAL ISSUES AND
POLICY MECHANISMS TO ADDRESS THEM***



Congress of the United States
Office of Technology Assessment
Washington, DC 20510-8025

Madam Chairman and members of the Committee, it is a pleasure to appear before you today to discuss the ethical, legal, and social implications of the Human Genome Project. The increased availability of genetic information offers the promise of improved diagnoses and therapies for genetic disorders and increased understanding of gene-environment interactions. At the same time, these scientific achievements have raised important ethical, legal, and social questions about the optimum use of such developments.

Since 1981, the Office of Technology Assessment has conducted more than a dozen assessments related to advances in biological research and human genetics. My remarks draw on several of these reports, including *Biomedical Ethics in U.S. Public Policy*, *Protecting Privacy in Computerized Medical Information*, *Cystic Fibrosis and DNA Tests: Implications of Carrier Screening*, *Genetic Counseling and Cystic Fibrosis Carrier Screening: Results of a Survey*, *Genetic Tests and Health Insurance: Results of a Survey*, *Genetic Witness: Forensic Uses of DNA Tests*, *Genetic Monitoring and Screening in the Workplace*, and *Mapping Our Genes--The Human Genome Projects: How Big? How Fast?*. As you requested, my statement first identifies some of the broad societal issues that have arisen as result of our rapidly growing knowledge of the human genome. It then reviews possible policy mechanisms to assess the impact of this knowledge.

Issues to Consider

Seeking to learn what the future holds is an enduring human quality. Folk ways once enjoyed wide favor in medicine, but over the years technology has increasingly eclipsed such methods of divination. The mysteries of biological inheritance--first explored by Austrian monk Gregor Mendel over a century ago--are yielding to modern science. Today, medical technology includes genetic tools that can deliver predictive information with ever-increasing accuracy. The ever-expanding array of genetic tests raises important questions for individuals and society.

Because compiling a list of the entire range of ethical, legal, and social implications raised by the Human Genome Project would be a daunting, if not impossible, task, my testimony focuses on an overview of six issues that OTA has identified in its reports as being important for Congress to consider. Even then, this testimony does not represent the full scope of OTA's analyses of the potential impact of knowledge gained from the Human Genome Project. In particular, I will focus on:

- professional capacity and continuing education,
- quality assurance of genetic service laboratories and genetic tests,
- privacy considerations of DNA databases and genetic research,
- reproductive issues,
- discrimination, and
- genetics education and the public.

Before briefly addressing these issues, however, I would like to mention one issue that nearly engulfs any discussions about genetic tests and the ethical, legal, and social issues they raise. I am referring, of course, to the issue of access to health care and health insurance reform, which I do not discuss in any detail because of the large and complex nature of the problem and because the issues generally are not unique to genetics. Suffice to say, access to genetic tests and the services related to them are inextricably linked to the broad issue of health care reform in the United States.

Professional Capacity and Continuing Education

For some individuals, even considering whether to undergo genetic screening or testing constitutes a potential life crisis because of the possible outcomes. Genetic counseling is an essential component of genetic screening and testing. It is a clinical service that includes providing an individual (and sometimes his or her family) with information about heritable conditions and their risks. Genetic counseling involves both education and psychological

counseling to convey information about the ramifications of possible test outcomes, prepare the client for possible positive or negative analyses, and discuss actual test results.

Many types of health professionals perform genetic counseling: physicians, Ph.D. clinical geneticists, master's-level genetic counselors, nurses, and social workers. Genetics training and continuing education for health care professionals is a critical policy issue today, but looms even larger for the future. As information from the Human Genome Project accumulates, the need for health care professionals with adequate knowledge of human genetics will be exacerbated.

The adequacy of trained personnel to handle the potentially exponential increase in patients in need of genetic counseling is a matter of debate, and OTA has reached no conclusion about whether increased numbers of genetic specialists are necessary. What is clear, however, is that increased genetics education for all health care professionals is desirable and likely will be necessary. Yet, Federal support for genetic services, education, and training has declined precipitously. In our August 1992 report, *Cystic Fibrosis and DNA Tests: Implications for Carrier Screening*, OTA found that funding for such activities under the Maternal and Child Health block grant had declined 76 percent (in real purchasing power) between 1981 and 1990.

Quality Assurance

Quality assurance of genetic tests means ensuring the safety and efficacy of the tests themselves, whether they are performed de novo in clinical diagnostic laboratories or via test kits.

Quality assurance to assess clinical laboratories' performance in genetic testing remains in flux. Under the Clinical Laboratory Improvement Amendments of 1988 (Public Law 100-578), Congress directed the Health Care Finance Administration (HCFA) to oversee the estimated 300,000 to 600,000 physician, hospital, and freestanding laboratories. To date, however, HCFA

has yet to classify many genetic tests or to detail particular performance standards for their conduct. Nor has a mandatory proficiency testing program for DNA-based analyses been developed, although such programs exist for other clinical tests.

With respect to diagnostic genetic tests, the Food and Drug Administration (FDA) regulates test kits under its authority to regulate medical devices. Though FDA also could regulate reagents currently used in DNA-based assays, it does not and likely will not. Facilities may develop such reagents into analytical procedures and then offer DNA-based tests as clinical services. This practice and the facilities that conduct the tests--but not the reagents--would be regulated by HCFA. Because the development of DNA-based diagnostic kits is in such an early stage of development, it is difficult to assess whether FDA's current regulatory oversight for DNA-based tests is adequate, or whether modifications are necessary.

Privacy Considerations of DNA Databases and Genetic Research

The increased availability of genetic information raises several questions with the theme of privacy. And, although I only briefly touch on two areas, I would like to emphasize that the issue of privacy is broad ranging and diverse.

The pervasive use of computer systems to collect personal information, including genetic information, raises civil liberties issues and informational privacy concerns on many levels. For example, in the arena of forensic DNA analysis, at least 34 states have laws (or legislation pending) that allow the law enforcement community to maintain computer databases that include genetic information (or store biological samples for future analysis) on certain individuals. In medicine, computerization of health care information, including genetic status, offers new opportunities to improve and streamline the health care delivery system, but also presents new challenges to individual privacy interests in personal health data. Since computer databases that contain personal, genetic information will only increase with time, the policy ramifications of maintaining confidentiality and protecting the privacy rights of individuals also will escalate.

The issues of privacy and confidentiality are also important to ongoing and future genetic research. One of the essential approaches used to map disease genes involves the use of biological material from large numbers of family members to trace the inheritance of a specific trait. Yet the very nature of such studies can mean that participants might learn information about other family members, not just themselves. Superimposing concerns about privacy on a situation where individuals likely already have anxiety about their genetic status presents a challenge to researchers and policymakers.

Another area of genetic research where privacy questions are--and increasingly will be--important revolves around existing stockpiles of biological material (e.g., samples from family studies or pathology specimens from breast cancer patients). The extent to which researchers may use stored samples for purposes other than that for which informed consent was originally obtained is a matter of ongoing controversy. Balanced against the possibility that such samples can be key to new medical diagnoses and treatments is the need to respect the rights of the donors.

Reproductive Issues

Fundamental to consideration of the application of many genetic tests is the issue of abortion. Depending on the specific genetic condition, prenatal screening or testing will comprise the primary use. Some tests will be more likely than others to have prenatal applications, but as long as utilization of these assays by pregnant women is possible, some will opt for abortion. Thus, the extraordinary friction about abortion in this country becomes inevitably linked with certain uses of genetic tests.

Furthermore, the social, ethical, and political tension extend beyond the use of tests by pregnant women to encompass certain avenues of basic research. Only last week, an NIH advisory panel issued its deliberations on the area of embryo research. Among the recommended areas for restricted federal funding for certain types of embryo research was preimplantation

genetic diagnosis. The controversy that surfaced with the release of this report is indicative of the type of contention that will continue to surround certain genetic tests and research for years to come.

Discrimination

Stigmatization of, or discrimination against, persons with certain diseases is not unique to illnesses with genetic origins. Yet as the number and scope of predictive genetic tests increase, so do concerns about perceptions of and behavior toward people who have genetic disorders (or have predispositions or are carriers for them).

One of the most sensitive issues raised by the Human Genome Project is the extent to which increased knowledge about genetic status will lead to (or exacerbate) discrimination in the workplace and access to health care. And, much of the recent focus in this area has centered on the Americans With Disabilities Act (ADA; Public Law 101-336).

As enacted, the ADA left open the question of whether genetic predisposition to illness or carrier status were covered as protected classes. Additionally, the ADA is silent on whether employers may discriminate--for the purposes of hiring--against people who are perceived as more likely to incur extra health care costs due to illnesses that could occur in their future children, even though the individual does not have the genetic condition (i.e., he or she is a carrier). Because the Equal Employment Opportunity Commission asserted that the ADA does not protect individuals based on genetic status alone (i.e., people who are carriers, have a predisposition to a genetic disorder, or who are presymptomatic), concerns about discrimination are unlikely to dissipate.

Public Education about Genetics

The need for better scientific literacy has been a topic of wide discussion for several years, and education about human genetics is, in many respects, no different. Increased public

education in genetics would benefit individuals' perceptions and understanding about genetic test results. Public education can go a long way toward preparing individuals for a decision on whether or when to seek genetic testing. Moreover, only through better public education will Americans appreciate that the increased availability of genetic information extends beyond medical implications--carrying social consequences, as well. And finally, public education might also exert an influence on the degree to which genetic status is perceived as a discriminatory or stigmatizing factor.

The value and importance of increasing public understanding of human genetics cannot be overstated. Yet, public education programs targeted to genetic diseases have been nearly nonexistent since those established under the 1976 National Genetic Diseases Act (Public Law 94-278) were phased out in 1981.

Policy Mechanisms

Since fiscal year 1988, when Congress and the executive branch first made a commitment to fund the Human Genome Project, concern has been raised about the mechanisms by which the ethical, legal, and social issues the project raises would be identified and explored, and then appropriate remedies reviewed and implemented. To address such considerations, the National Institutes of Health and the U.S. Department of Energy each funds an Ethical, Legal, and Social Issues (ELSI) program. Funds for each agency's ELSI effort derive from a set aside of 3 to 5 percent of appropriations for the fiscal year's genome initiative budget.

The ELSI programs fund research related to the Human Genome Project in order to expand the knowledge base in the broad area of genetics and ethics, law, and social and public policies. The programs operate independently in the model of peer review competition for grant funds. The ELSI Working group, which is a joint NIH-DOE effort, advises both programs; initially, it framed the agenda and established priority research areas.

Nevertheless, the nature of grant programs means the ultimate direction evolves from the bottom up--i.e., from the individual perspectives of researchers pursuing independent investigations--rather than from the top down--i.e., through policymakers or an overarching federal body. Furthermore, no formal mechanism exists for ELSI-funded research findings to directly make their way back into the policy process. Despite the recommendation of at least two successive Congresses that the National Center for Human Genome Research (NCHGR) adopt a commission-like mechanism with adequate staffing to examine and implement guidelines or recommendations derived from its ELSI grant portfolio, no such entity has materialized. In the past few months, however, NCHGR has moved to expand its policy analysis capacity. Thus, the extent to which any implementation of ELSI Working Group recommendations moves forward is currently in flux.

Regardless of the approach and structure that NCHGR, DOE, and the ELSI Working Group ultimately adopt, at least one other mechanism is under development that could provide the opportunity to assess the impact of the Human Genome Project and make policy recommendations.

In part in response to the OTA report, *Biomedical Ethics in U.S. Public Policy*, which drew attention to the important impact on U.S. public policy by most bioethics commissions, the White House Office of Science and Technology Policy (OSTP) published a draft charter for a proposed National Bioethics Advisory Commission (NBAC) in the August 12, 1994 *Federal Register*. Additionally, the Department of Health and Human Services and the Department of Energy sent letters to OSTP encouraging the development of such an effort.

NBAC, if constituted, could provide a high profile, cross-agency forum to address some issues pertinent to the Human Genome Project. For example, the draft charter includes the direction that, "as a first priority, the Commission will direct its attention to consideration of issues in the management and use of genetic information;" such a study is only one of two

directly identified as NBAC topics. Moreover, NBAC recommendations may carry significant weight by virtue of the position the commission occupies in the executive hierarchy.

Additionally, the draft charter contains language that compels departments and agencies to respond to any NBAC recommendations. The draft NBAC charter states that "[t]he Commission may specifically identify the Federal department, agency or other entity to which particular recommendations are directed and request a response from the Federal department, agency or other entity within 180 days of publication of such recommendations." In other words, should the agency opt not to implement an NBAC recommendation, the agency must publish public notice that details the reasons it is not doing so. OTA found such a "forcing clause" to be an important factor in the effectiveness of past bioethics commissions.

Still, NBAC clearly is positioned to undertake work that is of policy interest to multiple agencies; such an authority and purpose is expressly stated in the draft charter. Thus, some items important to policy analysis and implementation related to the Human Genome Project might be viewed as too narrow for NBAC to undertake. Hence, it will be important to examine the relationship between NBAC, the ELSI Working Group, and NCHGR's intramural policy analysis capacity. Because none of the entities is in place in its likely future form, however, it is impossible to speculate further about how this landscape will shape up.

Of course, Congress itself could create a new bioethics commission that incorporated some or all aspects of NBAC, and Congress could designate which issues such a body could address. Congress also could direct by statute that NCHGR and DOE adopt certain procedures to increase their Human Genome Project-related policy analysis capabilities; previous recommendations were made as report language to appropriations legislation and via a committee report.

Summary

Madam Chairman, as was my task, I have described several ethical, legal and social issues that information from the Human Genome Project might raise. I do not want to leave the impression, however, that OTA has not considered the potential opportunity and many positive features the project can offer; in fact, we have reported on these facets elsewhere. What is important is striking a balance between our intellectual curiosity in pursuing an exciting line of inquiry--one that will lead to medically important applications--against our obligation to see that the applications of any information gained are ethical and legal.

No one can estimate in common terms what it means to an individual to possess information about his or her genetic status. As our knowledge of the human genome increases, what we do with genetic information will depend on the perceptions, beliefs, and values of all Americans. Public understanding of this new knowledge and its implications is necessary for its wise and thoughtful application.

Again, OTA appreciates the invitation to discuss the important issues raised at this hearing, and I will be happy to answer any questions.

Mrs. LLOYD. Thank you very much, Dr. Nishimi. We appreciate your testimony as well.

I'm going to begin with you and ask you, in light of your testimony, do you believe that we should limit information on genetic research to individuals or their access to genetic testing? You've all discussed it, what it can do, what it can't do.

It seems to me at this stage, we are looking 20 years from now, Dr. King, we may—or 10 years might have a different viewpoint. But at the present time, knowing that there's—there's so much that we don't know, is there more harm to be done and less good to be gained by releasing this type of information?

Dr. NISHIMI. In our report on cystic fibrosis, OTA concluded that it was important for people to be afforded the opportunity to decide for themselves, recognizing, of course, that a lot of education would be needed for them to make informed and reasoned choices.

Mrs. LLOYD. But what I'm referring to, not all individuals—and I'm not putting anyone down because I'm not sure that I do—have the ability to assimilate and use this information.

Dr. NISHIMI. Sure. As a matter of record, OTA has not come out in favor of totally eliminating the—let's see, the use of genetics, genetic tests and the information that they offer, no.

Mrs. LLOYD. Dr. Clayton, what is your response?

Dr. CLAYTON. My response is that in general, I, too, favor making genetic information available with—with clear explanations of what the limitations of its usefulness are. There is a long-standing debate about when information becomes useful enough to be sharable, and this is a real—this is a really difficult issue. I would say, in general, I'm concerned when we decide not to share information, but I'm even more concerned when we share it and don't tell people what it means.

Mrs. LLOYD. Thank you.

Dr. Holtzman, I think you really touched on this in a beautiful manner in your testimony that these tests are being abused and not used in some instances.

Dr. HOLTZMAN. That's correct. I think that your question is a— a very important one and one which ultimately must depend on the decision of the individual as to whether he or she wants a test. But one of the problems today is that, as you paraphrased me, these tests are being abused and that they are being offered to people without adequate validation and by professionals sometimes who are inadequately trained to communicate the risks, as well as the benefits, of the tests.

And I think that we do need policies that will assure that when tests become available—and I think once their safety and their benefit is established, they should and will become available. But I think until we've reached that point, that there is a danger in making them available prematurely. So even for the breast cancer tests, as Dr. King eloquently mentioned that today, what we need is really still a research venue to offer these tests so that we can learn more about their risks as well as their benefits.

Mrs. LLOYD. Do you feel that we should adopt more stricter Federal standards to limit the number of laboratories that—or hospitals that might be involved in genetic testing?

Dr. HOLTZMAN. Well, yes, I do. I think that, as I said in my testimony, in terms of laboratories, the Clinical Laboratory Improvement Amendments, which require laboratories to register with HCFA and to develop proficiency programs or to participate, participate in proficiency programs, provides a very good framework for developing adequate standards. The problem has been that there is no genetic specialty recognized as such in the rules under CLIA.

CLIA has established a number of laboratory specialties, none of them genetic. There is one that relates to chromosome tests, but there really has been continuing silence on the matter of establishing a genetics specialty and developing proficiency programs, requirements for laboratory personnel, for interpretation of test results, all of which HCFA has the authority to do under CLIA, but it hasn't been done in the area of genetics.

Mrs. LLOYD. I'm especially concerned, Dr. Clayton, when you were referring to the tissue samples which would be retained. Do you feel that there is also a need to further restrict the ability of releasing this information or doing further testing?

Dr. CLAYTON. In an identifiable form, yes.

Mrs. LLOYD. Yes.

Dr. CLAYTON. Let me follow up on Dr. Holtzman's statement, if I may.

This problem of people—of professionals offering tests without adequate disclosure of the implications is not, however, unique to genetics. As a primary care physician, screening is what I do for a living, and—that's a—that's a little more broadly stated than I really mean. But I think that physicians, for a long time, have tended to think that screening is an unmitigated good and have failed to realize the larger consequences of screening.

So I think that we would make a mistake if we—if we sort of singled out genetics, genetic tests for this kind of scrutiny and ignored the other kinds of testing that could go on in medicine.

Mrs. LLOYD. Would you further expand on that.

Dr. CLAYTON. Okay, I'm going to expand on it.

Mrs. LLOYD. Right.

Dr. CLAYTON. There was a recommendation earlier this year that all neonates be screened for hearing loss. And it turns out that the test that they were proposing to use would identify—one in 1,000 children have profound hearing loss. And this test would identify about somewhere between 20 and 50 out of 1,000 children as having hearing loss and they would be followed up.

So can you imagine what it would mean—mean to have this brand new baby, be told that your baby may be deaf. We can't tell you whether your baby's deaf until they are six months or a year old. And so there you are, you have this brand new baby and you think the baby may be deaf. In addition, there is very little evidence that diagnosing deafness before the age of six months in fact improves long-term outcome.

Now, this was a consensus statement offered by a consensus group at the NIH. I mean, I think that that's just a mistake. I'm a pediatrician, so I don't follow adult medicine very much. But certainly articles come out all the time about the utility of screening

people with—asymptomatic males with PSA and other things like that.

I think we need to take this whole issue of screening much more seriously and I think genetics, I think, fortunately brings it very much to the fore that we can consider it. But we ought not to sort of tar genetic tests and let everything else go off scot-free. I happen to know he wholeheartedly agrees.

Mrs. LLOYD. Dr. King, everybody has had their turn, so I will let you wind up the question.

Dr. KING. Thank you.

Those of us working in breast cancer research for the last decades have, of course, had the privilege of working with families in whom the disease is very common, and I must say that the experience of my group is that we tell the members of those families who wish to know everything about our work and about the consequences of that work for that particular woman. Obviously we don't share information about relatives with each other, but every woman in our project knows everything that she wants to know about her own situation.

Now, clearly that kind of intense friendship that develops over 20 years of working together has to evolve when tests move from a personal research setting into a clinical setting. And with that evolution and that transition in mind, Francis Collins, as Director of the National Center for Human Genome Research, suggested some months ago, that the NCHGR, the National Cancer Institute, the National Institute of Nursing Research and probably several others that I managed to forget altogether and fund jointly about a dozen research programs that would undertake to answer the questions that you have been asking: How can we take this information, which is available now, to be used for screening, make sure that the quality of the technical information is good, make sure that it's communicated in a way that is useful, make sure that women who can—who can use the information, given their own family histories, are in a position to obtain it, but that marketing frenzy doesn't—doesn't take over the field.

And just a couple of days ago, 11 institutions scattered around the country and representing women's—women with very different kinds of backgrounds have been funded to undertake these research protocols. So what I am looking forward to is learning from my colleagues in those 11 institutions what they find to be the most effective and the most useful ways of taking the new scientific information, the new genetic information and either limiting its use or opening its use in various contexts. So, as usual, what we gain is collective experience in the field.

Mrs. LLOYD. Any other comments you would like to make on the subject? We mainly—Dr. Nishimi, I didn't—

Dr. HOLTZMAN. May I just make a comment in relation to that?

Mrs. LLOYD. Yes, sir.

Dr. HOLTZMAN. I think one critical thing, and Mary-Claire pointed to this, is that in the involvement in determining where we go from here in genetic testing that we really have an opportunity to develop, which may sound surprising but I think it is a new paradigm in bringing new technology to the public, and that is the matter of involving consumers, patients, if you will, in developing the

kind of information that they feel, as well as physicians feel, should be included.

And one of the studies under the Breast Cancer Consortium that Professor King just mentioned is being done by a colleague of mine at Johns Hopkins, Gail Geller, where we intentionally will be asking consumers, both women and men, in the general population and those that are at high risk of breast cancer what it is that they want to know.

And this whole notion of trying to break down what I think has been a barrier in communication between physicians on the one hand and patients on the other, I hope, will with research—and clearly this is not only our group who are doing it—will be broken down by learning more and involving consumers more in learning how new technology should be used.

Mrs. LLOYD. Well, it seems to me at this stage of genetic research it is so important that what is done and your communications with the public be done well that we—that we don't do unnecessary testing, that we do communicate to the public what this means and what it can do. We don't want some well-meaning person to get on television and talk about the evils of genetic testing. We want to make sure that what we do is right. And I would urge all of you to be very wary of what a lack of knowledge can mean so many times.

One of the things that we—we discussed is health insurance. Are there other issues that are resulting from this project that people are very concerned about, as well?

Dr. King?

Dr. KING. Could I take this on? And I speak here as a geneticist and citizen and not as a physician. Were I a physician, I probably would not have been as naive as I were when this event occurred. A young woman named Jan in one of the families with whom I worked in the 1970s became involved in our project in a very dramatic way.

Jan's mother was 53 when I first met her and her mother had survived a breast cancer first diagnosed at the age of 36. And the mother was one of 18 women with breast cancer in this family. And the mother had been a part of the project since it first began, and had, as we got closer and closer to the gene, a very interesting genome type. Jan was at that time 27. This was last year.

And I asked the mom if she would ask Jan if Jan would give us a blood sample as well—Jan was completely healthy, well, doing beautifully, just had her second child—so that we could determine if this interesting genome type in the mother had been inherited by Jan. And Jan said sure, she would be happy to. So she went to her mother's physician, her mother's surgeon, indeed, to have the blood drawn. And he did. That was terrific. Sent the blood out to us, took the DNA.

Then he said, while you are here, Jan, even though you are only 27, given that you have 18 relatives with breast cancer in the family, let me do a mammogram for you. And at that age, obviously she had never had one before. But she has breasts that are susceptible to—to good mammographic analysis, which many 27-year-old women do not, but she does.

So he did a mammogram and picked up a lesion. He had not felt it on palpation. Once he knew where to feel, he could feel it, but it was small and her breasts are large. It was a small lesion. Her immediate reaction was not either "Oh, my God, I've got breast cancer," or, "Thank goodness you found it this early, but I haven't got any insurance. I can't afford the surgery."

So the reaction of the surgeon, who is a remarkable person in Southern Illinois, was to organize the Catholic Charities, the Illinois American Cancer Society, the local hospital, his own team so that they put together a package so that this one person could get absolutely standard therapy that was nothing remarkable or exotic about what she needed. She needed a simple—she needed a lumpectomy followed by radiation.

She had the surgery. She's doing beautifully now in the next year. There's no question about it but that she will do very well. My point is that it doesn't do us any good at all—oh, and incidentally, she did have the interesting genome type of her mother and she was indeed susceptible to developing breast cancer. It didn't do us any good to do all the most lovely, molecular biology one could possibly imagine with this family if we can't get standard therapy to women who need it when their breast tumors are diagnosed. So in the absence of insurance reform and health reform, molecular genetics is essentially meaningless.

Mrs. LLOYD. That's a beautiful, beautiful story. Any further comments?

One of the things that was—that has come to my attention in this report of the Institution of Medicine that was funded by DOE and NIH genome there may be a conflict of interest on those in a position to recommend tests—I see you smiling, Dr. Holtzman—and their financial interests in laboratories.

Would you like to comment on potential conflicts of interest and how can we monitor this?

Dr. HOLTZMAN. Well, this, again, is not an issue that's unique to genetics and has prompted the American Medical Association to publish, I guess, guidelines regarding referrals that physicians may make to their own laboratories saying that this has to be completely in the open.

I think that it's a very difficult situation, perhaps more difficult in genetics where much of the information that is given—and I'm referring here to genetic testing for reproductive purposes, either for prenatal, referring a woman for prenatal diagnosis or for character testing as a possible preliminary for prenatal diagnosis. But this is an area in which the standard that has evolved among geneticists is one of respecting the woman's autonomy and of not being directive in telling the woman or making a recommendation to the woman that she have such a test.

Now, it seemed to the Committee that this becomes difficult to do, to follow that standard of nondirectiveness, when in fact the genetics counselor's salary may be, in part, derived from the revenues from the test itself. That is, most of the source of income of laboratories to pay for counseling doesn't come from the counseling, per se, in terms of what the reimbursement level is but from the laboratory tests.

So it's a very difficult issue that certainly as of minimum I think needs to be explained, that sources of income need to be explained to women. But I think there is an interesting solution as genetic tests in this area, provided that they are offered in a safe manner, will make this less of a problem. That is in this area of primary care physicians who more and more are going to be offering genetic tests are going to be less and less likely to have such conflicts of interest.

So it seemed to the committee and seems to me personally that perhaps we don't need a whole lot more geneticists and genetic counselors operating in separate specialties, but what we really need is—and this is only a small reason to justify this, more primary care physicians who will learn enough genetics and largely, because if you look at the standards on which primary care should operate, these are physicians who know their patients, have a continuing relationship with them and could communicate to them over a period of time the benefits and risks of things like genetic tests and theoretically could do it in a more autonomous way, with a greater respect for autonomy perhaps than people who've a vested interest.

Mrs. LLOYD. Your colleagues are nodding.

Dr. CLAYTON. Well, my only thing I'm nodding about, as a primary care practitioner in Tennessee who takes care of primarily—of Tenn Care patients who works in a capitated care system, the problem is our conflict of interest is going to be in the other way, namely that if one gets capitated fees, and you know that if you offer tests, that comes out of the money that you are being paid to take care of the patients. In fact, it just—the incentive is in the other direction. I do think that primary care physicians are a good thing. But I think that that's not, unfortunately, always going to be the answer.

Mrs. LLOYD. Dr. King? Dr. Nishimi?

I want to thank you for a very, very interesting and well-documented presentations. I've never had a finer panel. And I certainly thank you for being here. I do apologize that we've had multiple votes this afternoon. These are procedural votes. But I want to ask your indulgence and we will be submitting questions in writing. I'd like for you to supply your answers for the record.

And I want to thank our staff and Tina Van Sickle, all who've worked so hard, Harlan, thank you, Dr. Watson, you have all worked very hard. Thank you very much. And we wish you well.

The subcommittee stands adjourned.

[Whereupon, at 3:31 p.m., the subcommittee was adjourned.]

APPENDIX



Department of Energy Washington, DC 20585

December 8, 1994

The Honorable Marilyn Lloyd
Chairman
Subcommittee on Energy
Committee on House Science, Space,
and Technology
U.S. House of Representatives
Washington, DC 20515

Dear Madam Chairman:

On October 4, 1994, Dr. Ari Patrinos, Director, Office of Health and Environmental Research, Office of Energy Research, testified regarding the Department's Human Genome Project.

Enclosed are the answers to 13 questions submitted by you to complete the record.

If we can be of further assistance, please have your staff contact our Congressional Hearing Coordinator, Renee Wilhite, on (202) 586-4273.

Very truly yours,

A handwritten signature in dark ink, appearing to read "William J. Taylor, III", is written over the typed name.

William J. Taylor, III
Assistant Secretary
Congressional and Intergovernmental
Affairs

Enclosures



Printed with soy ink on recycled paper

QUESTIONS FROM CHAIRMAN LLOYD

Question #1: DOE is utilizing a number of DOE labs in the conduct of the human genome project. How does DOE decide on the allocation of tasks and funding that goes to the labs?

Answer: DOE funds human genome centers at Los Alamos National Laboratory, Lawrence Livermore National Laboratory, and Lawrence Berkeley Laboratory, as well as individual projects conducting human genome research at these and five other DOE Laboratories. Funding for the three genome centers was initially provided following peer review of proposals submitted by these Laboratories. These proposals focused on the multidisciplinary strengths and capabilities that these Laboratories could employ to address the critical needs of the human genome program in mapping, sequencing, informatics, and for the associated development of needed technology in each of these areas. The DOE Human Genome Centers undergo regular, peer review site visits that are used to evaluate both the quality of the science conducted at each Center, as well as to ensure that critical genome program needs are being met. Funding decisions for all projects at DOE Laboratories that are not part of a Genome Center are based on the scientific peer review of individual proposals, as part of a panel review. Meritorious proposals undergo a programmatic evaluation by the Human Genome Coordinating Committee, a group of senior DOE-funded scientists from universities and DOE National Laboratories with expertise in the various areas of research found in the genome program, and the DOE program staff to identify those proposals that address critical genome program needs.

How does DOE decide on the amount of funding that goes to universities?

Each year the DOE Human Genome Program publishes guidelines for the submission of grant applications for genome research in the Federal Register that outlines the current research needs of the Program. The announcement also identifies the total funds that are available for new research for each solicitation. Total funding levels for research conducted at universities are not predetermined. Funding decisions for all research conducted at universities are based on the scientific peer review of individual applications, as part of a panel review. Meritorious proposals undergo a programmatic evaluation by the Human Genome Coordinating Committee and the DOE program staff to identify those proposals that address critical genome program needs.

Is university participation conditioned on their participation in the multidisciplinary efforts conducted at the labs and genome centers?

Funding of genome research at universities is not contingent on the participation of individual investigators in the multidisciplinary efforts conducted at the DOE Laboratories and Genome Centers. However, university investigators are encouraged to collaborate with scientists at DOE Laboratories and to take advantage of, or utilize technologies developed at DOE Laboratories to benefit their own research efforts. Interaction between investigators at universities and DOE Laboratories is further encouraged by

- the conduct of meetings, workshops, and contractor meetings that are attended by all investigators funded by the DOE Human Genome Program.

To what extent does DOE fund individual investigator research at universities that may not be affiliated with the multidisciplinary efforts at the labs and genome centers?

Genome research funded at universities runs the entire spectrum from being tightly linked to and dependent on research at DOE Laboratories and Genome Centers, to developing technologies that will be utilized by DOE Laboratories and Genome Centers, to being completely independent from research at DOE Laboratories and Genome Centers. However, the targeted nature of the DOE Human Genome Program results in a natural linkage between investigators at different universities and at DOE Laboratories so that no project exists entirely independently of any other project.

What is the internal and external review process that ties all of these performers together to achieve a coherent program to meet the five year goals?

Results of all genome research are regularly presented and discussed at DOE genome contractor and grantee meetings so that all investigators are exposed to all ongoing research in the Program. The Program, both ongoing research, proposed research, and future research needs, is also regularly discussed and evaluated by the Human Genome

Coordinating Committee, the genome subcommittee of the Health Effects Research Advisory Committee, and by the DOE Human Genome Program staff to maintain and evaluate both the focus and the progress of the Program.

Is the process "bottom up" or "top down" with respect to funding decisions?

Funding decisions are based on the combination of scientific peer review of research applications by review panels and the subsequent evaluation of the most meritorious applications by the Human Genome Coordinating Committee and the DOE program staff for programmatic relevance and their ability to meet critical research needs. Final funding decisions are made by DOE Human Genome Program staff. These reviews and evaluations ensure that available funds are used to support the highest quality research that best enables the genome program to achieve its stated goals. This process could be characterized as "top down."

Question #2: Please explain the peer review process that is used to choose proposals for funding. Are lab proposals reviewed separately? Are individual investigator proposals reviewed separately?

Answer: The DOE Human Genome Centers undergo regular, peer-review site visits that are used to evaluate both the quality of the science conducted at each Center as well as to ensure that critical genome program needs are being met. Funding decisions for all projects at DOE Laboratories that are not part of a Genome Center are based on the scientific peer review of individual proposals, as part of a panel review. Meritorious proposals undergo a programmatic evaluation by the Human Genome Coordinating Committee and the DOE program staff to identify those proposals that address critical genome program needs. Similarly, research applications submitted by university investigators in response to annual announcements in the Federal Register that outline the current research needs of the Program undergo scientific peer review, as part of a panel review, and programmatic evaluation by the Human Genome Coordinating Committee and the DOE program staff. Individual investigator applications from universities and DOE Laboratories are reviewed separately by the same review panels.

How are evaluators chosen for peer review panels?

Reviewers are chosen for peer-review panels based on their scientific expertise in the areas represented by the applications being reviewed. Panelists do not have research

applications being considered by the panel of which they are a member. All panelists are required to sign conflict of interest and confidentiality statements assuring that they do not have any affiliation, personal, or financial connection with the institution or the person whose application they are reviewing, and that they will not divulge or use information from the application. On occasions where potential conflicts of interest exist for individual reviewers and applications, the reviewer will leave the room during the discussion of the application in question.

How do you incorporate the goals of objectivity and knowledge into the peer review process?

Objectivity and knowledge are incorporated into the peer-review process through the use of independent experts on the scientific review panels. The ability of individual research applications to contribute to the long-range goals of the genome program is evaluated by the Human Genome Coordinating Committee and the DOE genome program staff. A testimony to the success of this two-tiered system of scientific review and programmatic evaluation is the fact, noted in the press, that the genome program is well ahead of

schedule for completion of its initial five-year goals. A new five-year plan was published in 1993, and recent progress indicates that the program is ahead of schedule for these goals as well.

Question #3:

To what extent is DOE encouraging meetings, seminars and other discussion forums with the public, not just other decisionmakers, to stimulate thoughtful public debate of these issues?

Answer:

A major aspect of the DOE Human Genome Program's Ethical, Legal, and Social Issues (ELSI) Program is the sponsorship of a wide variety of educational programs, including meetings and seminars. DOE has recently sponsored two highly acclaimed public television programs on genome issues. DOE has also sponsored a judges' workshop for trial judges to receive information on and discuss the use of DNA evidence in the courtroom. The genome program has also sponsored conferences or workshops that: (1) considered discrimination that could result from the use of genetic information about ethnic and other groups; (2) considered genetics, religion, and ethics; (3) provided public officials and other nonscientists hands-on experience with genome-related technologies; and (4) provided hands-on genome experience to high school teachers. Workshops for policymakers and opinion leaders are also sponsored.

What educational materials have been developed for the public regarding the human genome project. What has been the impact of such outreach and information?

Educational materials produced with funding from DOE's Human Genome Program have been far more successful and have had a greater impact than could have been anticipated. By far, the most successful has been the Primer on Molecular Biology that was sent to every high school biology teacher in the

country. More than 30,000 copies have been distributed by DOE, and the number in use, given individual copies made by individuals and schools, is far greater. This primer is also available electronically on-line, and has been used to teach high school students, graduate students, and physicians at institutions such as Harvard and Stanford. Additional materials that have been or are being produced and distributed include a judge's desk reference on the use of DNA evidence, a high school curriculum on the human genome project in both English and Spanish, museum exhibits, and public television programs on the human genome program. The impact of these activities has been to increase awareness and sensitivity to the ethical issues associated with the genome program.

Question #4:

Please provide a list of seminars, conferences, or other technology transfer outreach efforts sponsored by DOE including DOE labs or participated in by DOE or DOE labs in the past two years.

Answer:

Technologies developed for mapping, sequencing, and informatics as part of the human genome project are of great interest to research scientists and to the commercial sector. As a result, there is always considerable interest in the wide range of specialized and general conferences, workshops, etc., that deal with these genome-related technologies. During the past two years, DOE sponsored at least 30 different conferences, workshops, or other activities at which genome technologies were discussed and shared with national and international participants from universities, DOE Laboratories, and industry. A list of these conferences, workshops, and other activities is below. The number of outreach efforts not directly sponsored by DOE in which the DOE Laboratories have participated cannot be estimated, but is likely to be far greater than the 30 referred to above.

1. Chromosome Coordinating Meeting and the Human Genome Mapping Workshop, November 7-10, 1993, Kobe, Japan.
2. 58th Cold Spring Harbor Symposia, June 2-9, 1993.
3. 3rd International Workshop on Identification of Transcribed Sequences, October 2-4, 1993, New Orleans, Louisiana.
4. U.S. Participation in the XVIIth International Congress of Genetics, August 15-21, 1993, Birmingham, United Kingdom.
5. Workshop on Sequencing by Hybridization, October 28-29, 1993.

6. Genome Sequencing & Analysis Conference, October 23-27, 1993, Hilton Head, South Carolina.
7. Chromosome 14 Workshop, June 10-12, 1993, Toronto, Canada.
8. Conference on DNA damage and its effects on DNA structure and protein recognition, August 1-4, 1993.
9. Chromosome 18 workshop, July 19-20, 1993, Nijmegen, The Netherlands.
10. Chromosome X workshop, April 24-27, 1994, Heidelberg, Germany.
11. Human Chromosome 7 workshop, May 20-22, 1993, Marburg, Germany.
12. E. Coli genome meeting, September 9-13, 1993, University of Wisconsin.
13. Chromosome 9 workshop, April 10-12, 1994.
14. Chromosome Y workshop, April 9-10, 1994, Cambridge University, England.
15. Chromosome 16 workshop, May 8-11, 1994.
16. Chromosome 1 workshop, March 25-27, 1994, Bethesda, Maryland.
17. Contractor-Grantee Workshop III, February 7-10, 1993, Santa Fe, New Mexico.
18. Chromosome 14 Workshop, September 1-3, 1994, Oxford, United Kingdom.
19. International Conference on system sciences on genome informatics, Maui, Hawaii, January 4-7, 1994.
20. Conference on transcribed sequences in the human genome, October 16-18, 1994, Montreal, Canada.

21. International conference on Bioinformatics and genome research, June 1-4, 1994.
22. Workshop on process alternatives in technological controversies, October 6-7, 1994.
23. International mouse genome conference, November 6-10, 1994, London, England.
24. E. Coli meeting, November 4-8, 1994.
25. Chromosome 8 workshop, September 1994, Oxford, United Kingdom.
26. Conference entitled, "First World Congress in Computational Medicine, Public Health, and Biotechnology."
27. Conference on genome sequencing and analysis, September 17-21, 1994, Hilton Head, South Carolina.
28. Chromosome 7 workshop, October 14-17, 1994, Toronto, Canada.
29. Chromosome 3 workshop, May 13-14, 1994, Ann Arbor, Michigan.
30. Contractor-Grantee Workshop IV, November 13-17, 1994, Santa Fe, New Mexico.

Question #5: The human genome project is a large Federally funded research and development project. With such discoveries as the recently announced breast cancer gene, there may well be an increase in private sector funding of related research. How do you make sure there is no duplication with the private sector?

Answer: We can never be completely sure that research efforts sponsored by and conducted at private companies are not duplicating those sponsored by DOE. However, given the enormity of the overall genome effort, the substantial progress made to date by the DOE Human Genome Program, and the public availability of progress and information generated in the DOE Program, it would not make sense for a private company to knowingly duplicate ongoing efforts in the DOE Program. In addition, the DOE Human Genome Program office has considerable, regular contact with representatives from industries that are involved in or interested in genome information and technologies.

Question #6: A recent article in the Wall Street Journal alluded to a superchip technology developed by Argonne National Lab that was licensed to the private sector. To what extent is DOE tracking the commercialization of sequencing and related commercial offshoots of the human genome project?

Answer: Since rapid, high throughput DNA sequencing is a major goal of the human genome program, DOE tracks industrial contributions to and commercialization of sequencing and related technologies.

What can you tell us about the scale and nature of the industry that is emerging? Please provide the committee with a list of all private sector participants in the DOE human genome program, including an indication of the nature of the relationship to DOE's program, i.e., contractor, grantee, CRADA participant, part of a funded consortium, etc. Please indicate the dollar value of the project including Federal and non Federal contributions and the nature of the project?

During the past several years, DOE Laboratories have been involved in sequencing-related CRADAs with at least three companies: Lawrence Livermore National Laboratory with Applied Biosystems, Los Alamos National Laboratory with Life Technologies Inc., and Brookhaven National Laboratory with U.S. Biochemical. The largest of these CRADAs, and the only one that is currently active, is the two-year Lawrence Livermore National Laboratory/Applied Biosystems CRADA. In addition, the new superchip technology developed at Argonne National Laboratory was the basis for the formation of a new company, HiSeq, that will maintain ties with Argonne National Laboratory. The Advanced Technologies Program at the National Institute of Science and Technology recently announced \$56 million in new awards for industry-sponsored

development of DNA diagnostic technologies. Six of the 13 awards that were given included DOE genome scientists as nonindustrial partners. In addition, the DOE Small Business Innovative Research (SBIR) Program is currently funding three Phase I and three Phase II awards (see table below).

Private Sector Participation
in DOE Human Genome Program

<u>Participant</u>	<u>Funding Mechanism</u>	<u>Value or Dollars</u>	
		<u>Federal</u>	<u>Private</u>
Applied Biosystems (Lawrence Livermore)	CRADA	\$2.3M	\$4.8M
U.S. Biochemical (Brookhaven Natl. Lab.)	CRADA (Inactive)	\$ 18,000	\$15,000
Life Technologies, Inc. (Los Alamos Natl. Lab.)	CRADA (Inactive)	\$3.4M	Proprietary
Computational Biosciences	SBIR, Phase I	\$ 75,000	N/A
MacConnel Research	SBIR, Phase I	\$ 75,000	N/A
Molecular Machines, Inc.	SBIR, Phase I	\$ 75,000	N/A
Affymetrix, Inc.	SBIR, Phase II	\$500,000	N/A
Molecular Dynamics	SBIR, Phase II	\$500,000	N/A
Tropix, Inc.	SBIR, Phase II	\$500,000	N/A

Industrial interest in genome information and technologies is also apparent from the investments being made in genome related industries. Smith Kline Beecham recently invested \$125 million in Human Genome Sciences. Hoffman La Roche has invested \$70 million in Millenium. Bill Gates (of Microsoft) and a French consortium have invested a total of \$20 million in Darwin Molecular. All major drug companies are closely

monitoring progress in the genome program to identify potential impacts or benefits to their own interests. The recent initiative by Merck to develop a publicly available cDNA sequence database and the controversy surrounding some industrial efforts to patent these same sequences is a sign of the industrial interest in and enthusiasm for the human genome program, the information it is generating, and the technologies it is developing. Multinational companies such as Glaxo are also becoming high profile participants in Genome related efforts.

Question #7: Commercialization efforts can be expedited (or hindered) by a variety of policies relating to patents, licensing, rights in data, copyright, and protection of proprietary information and trade secrets, among others. Please describe how these policies govern commercialization efforts by the DOE labs, university participants, private sector entities, non profits, consortia or other entities that participate in DOE's human genome program through grants, contracts, cooperative agreements, CRADA's joint ventures or other mechanisms?

Answer: Legislation has been passed intended to facilitate the transfer of technology from DOE Laboratories and from universities to the private sector. This legislation generally gives the Nonprofit-operated Laboratories and universities first option to rights to patent products and technologies that they have developed. Laboratories operated by large businesses generally have similar access to patent rights, pursuant to class patent waivers that have been granted. Provisions are in effect in Laboratory contracts allowing contractors to assert and own copyrights in many circumstances, to facilitate technology transfer. Generally technical data arising from Laboratory research is publicly available and not proprietary, although in some circumstances, e.g., CRADA's, technical data can be protected from public dissemination for limited time periods to enhance technology transfer and commercialization. DOE Labs and universities generally have active technology transfer programs, including licensing, cooperative research and other mechanisms to interface with industry and enhance commercialization. Generally, the program office at DOE is not an active participant in these processes.

Please list the applicable statutory, regulatory, and other directives that govern DOE's policies.

Applicable legislation includes 35 U.S.C. 200 et seq.; 42 U.S.C. 5908; 15 U.S.C. 3710. Implementing regulations include 37 C.F.R. 401.

Question #8: What advisory group review has been conducted to date to determine the efficacy or hindrance of the commercialization policies noted above, on commercialization of results, products, technologies, methods, etc., from the human genome project?

Answer: No advisory group reviews have been conducted on commercialization policies, but the successes of the human genome program speak for themselves. When one considers the development of new Federal programs like the Advanced Technologies Program at the National Institute of Science and Technology, the large-scale investments that numerous companies are making in biotechnology, and the general scientific and commercial sector interest in the results and technologies of the human genome program, it is hard to imagine a more successful government project. The DOE Ethical, Legal, and Social Issues Program is currently funding a study at the University of Michigan Law School to study "The Role of Patents in Technology Transfer in the Human Genome Project."

It would seem that some of these issues could come under the rubric of the ELSI working group. To what extent will the ELSI group review such issues?

The Ethical, Legal, and Social Issues Working Group does not have specific plans at this time to study these commercialization issues.

Question #9:

One of the key capabilities of the DOE human genome effort is the multidisciplinary facilities in the DOE labs and designated genome centers. To what extent is NIH using these facilities for genome as well as other health related research including structural biology, etc.? Is NIH using other DOE facilities such as the ALS, NSLS, etc?

Answer:

An excellent example of the successful interaction between the NIH and DOE genome programs is the *Drosophila* sequencing project at the University of California at Berkeley. NIH is likely to fund a major, multiyear effort at UC Berkeley to sequence the genome of the fruit fly. This work will be funded by NIH, but will be carried out at the Lawrence Berkeley Laboratory Human Genome Center using sequencing technologies developed as part of the DOE Human Genome Program. Another large scale, highly successful collaborative effort between NIH and DOE is the NIH-funded national flow cytometry resource at Los Alamos National Laboratory. This resource brings advanced flow cytometry technologies to investigators at universities.

DOE's primary emphasis in its structural biology program is the development and support of user facilities for structural biology research at facilities such as the Advanced Light Source and the National Synchrotron Light Source. The principal users of these facilities receive their research funding from NIH and NSF. The extent to which non-DOE scientists use DOE structural biology facilities is illustrated in a survey conducted as part of the development of the new structural biology beamline at Argonne National Laboratory's Synchrotron Radiation Source, scheduled for

completion in 1996. This survey demonstrated interest from 112 investigators at 73 different institutions in the U.S. alone.

Please provide a list of the projects, collaboration efforts, etc., with NIH and identify the funding arrangements ("work for others" "matching") that is being used.

NIH and DOE both provide funds to a number of different investigators as part of each agency's genome and other research programs. In the genome area, staff members from both NIH and DOE attend scientific reviews and programmatic discussions that are part of each agency's decision-making processes. Considerable crosstalk occurs between genome program staff members at the two agencies to ensure that individual investigators are not double-funded to do the same work.

Is DOE funding any projects at any NIH facilities?

DOE has funded several investigators at NIH to conduct genome research. Currently, DOE is funding research at the National Institute of Environmental Health Sciences, through an interagency agreement with NIH, on the development and characterization of yeast vectors for cloning large pieces of DNA. Previously, DOE funded research at NIH, through an interagency agreement, to sequence expressed sequences.

To what extent is NIH building comparable facilities or capabilities, e.g., informatics, supercomputers, data storage, gene banks and libraries, to support its genome program?

DOE and NIH provide joint support for the major international Genome Database at Johns Hopkins University with DOE being the lead agency. The magnitude of information coming out of the human genome program is so large, as discussed in a 1988 National Academy report on the genome program, that there is a need for numerous, specialized, but interlinked databases. For example, each DOE Genome Center has its own database for sequence or map data; however, their data is also submitted to public databases. The NIH genome program does not support the development or operation of any large public databases with the exception of their contribution to the Genome Database noted above.

Question #10: Clearly, other nations are interested in human genome research. What competitive pressures does DOE see coming from other national efforts?

Answer: The human genome project is truly a collaborative, international effort to map and sequence the human genome. One example of DOE's support of this international effort is the Genome Database, funded by DOE and NIH. The Genome Database has worldwide nodes through which investigators around the world are able to both input and access information in this database. There is no question that there is strong international interest in the commercial aspects of genome-related information and technology, and that there will be competitive pressures at the international level to develop genome-related products and services.

How does DOE designate areas of research that are amenable to international collaboration and those that are not?

Progress in the genome program is driven by individual scientists and research centers working within the confines of the long-term goals of the genome project. As a result, DOE does not identify or preclude specific research areas that are or are not amenable to international collaboration. To the contrary, the extensive effort required to develop the map and sequence information called for in the project's long-term goals requires international collaboration. For example, the *C. elegans* genome project to map and sequence the genome of this important experimental worm is a joint effort between the U.S. and the United Kingdom that will

generate information useful in understanding information derived from the human genome project. The yeast artificial chromosome map of the human genome developed in France is also a resource used by genome investigators around the world.

How is DOE participating in HUGO?

The DOE genome program has extensive and regular interaction with the Human Genome Organization (HUGO). The president of the HUGO is a genome program grantee and a member of the Human Genome Coordinating Committee. In addition, a number of key DOE genome investigators are members of HUGO boards. DOE investigators and program staff also attend HUGO meetings.

Question #11: OTA noted in "mapping our genes" (page 169) that a special patent situation existed with respect to LLNL and LANL. How was that issue resolved? OTA noted in the same report that there could be varying patent policies for research at all agencies involved in genome projects. Has this situation been resolved? If so how? If not, why not?

Answer: While Lawrence Livermore and Los Alamos National Laboratories have historically had weapons research responsibilities, the "restriction" to contractor retention of inventions noted in the OTA report would not normally be applicable to genome research, since genome research is not likely to be conducted under weapons related programs. Therefore, there should be no "special patent situation" at Lawrence Livermore or Los Alamos National Laboratories on this issue. While there may be some variation in patent policies covering contractor-operated laboratories as compared to government-operated laboratories, in both cases technology transfer authorities are in place such that industry can interact with both types of laboratories.

Question #12: To what extent does DOE track collaborative joint ventures, licensing, or other arrangements between recipients of DOE funding and other foreign entities? To what extent does it exist, and what guidelines govern its conduct?

Answer: The DOE genome program office does not directly track international collaborative efforts involving DOE investigators. As a complicating factor, it should also be noted that most large pharmaceutical companies with collaborative and scientific interests in genome research are multinational companies often headquartered in the U.S.

Question #13: Your testimony speaks to the ability of this research to lead to better risk assessments. Can you give the committee some examples of how the research contributes to risk assessments and how DOE would use such information?

Answer: DOE believes that it is important and useful to be able to identify individuals who, because of their unique genetic makeup, are at increased risk for adverse health effects from exposure to energy-related materials. This capability would, for example, enable DOE to better monitor and protect its workers involved in various cleanup or production activities; however, this capability would also be directly exportable to many industries and to society in general. Information and technologies from DOE's Health Effects and Human Genome Programs are being combined to identify and characterize specific genes or groups of genes that dramatically increase an individual's risk. The predictive potential of this information will be tested in animal models, which have only recently become available, that can mimic specific human genetic makeups. Finally, this information will be coupled with anticipated developments from the Advanced Technologies Program at the National Institute of Science and Technology that will make large-scale, genetic diagnosis both feasible and economical. This type of risk information, for example, can be used at DOE sites to provide counseling or added protection to high risk workers in potentially high risk positions. This information could also be used by individuals to modify their lifestyle, e.g., they might choose to quit smoking, if they were identified to be at greater health risk because of their genetic makeup. Clearly, the development of these diagnostic

or predictive capabilities also raises numerous ethical, legal, and social issues that will continue to be addressed by DOE's Ethical, Legal, and Social Issues Program.

"HUMAN GENOME--ISSUES"
OCTOBER 4, 1994
ADDITIONAL QUESTIONS FOR THE RECORD

DR. HOLTZMAN:

- WHAT MAKES GENETIC TESTS DIFFERENT THAN OTHER CLINICAL TESTS? HOW MANY GENETIC TESTS ARE BEING GIVEN NOW AND HOW IS THEIR QUALITY AND EFFICACY CONTROLLED OR REGULATED? TO WHAT EXTENT ARE PEOPLE RECEIVING INACCURATE INFORMATION? IF APPROPRIATE REGULATIONS ARE NOT PUT IN PLACE TO ASSURE EFFICACY AND ACCURACY WHAT RECOURSE DOES AN INDIVIDUAL HAVE THAT MAY RECEIVE INACCURATE INFORMATION? WILL THIS BECOME A CONSUMER FRAUD PROBLEM IN THE FUTURE WITHOUT BETTER SAFEGUARDS?

WHAT HAS HAPPENED AS A RESULT OF THE RECOMMENDATIONS FOR IMPROVED LABORATORY QUALITY OUTLINED IN THE RECENT INSTITUTE OF MEDICINE REPORT "ASSESSING GENETIC RISKS"? IS THE HEALTH CARE FINANCE ADMINISTRATION SHOWING ANY INTEREST IN THE RECOMMENDATIONS FOR OVERSIGHT OF TESTING IN LABORATORIES? WHAT ABOUT FDA?

- HOW WILL AN INDIVIDUAL SORT THROUGH THE ADVICE OF THE NUMEROUS ASSOCIATIONS, MEDICAL ADVICE, AND MARKETING LITERATURE TO COME TO DECISIONS UNDER UNCERTAINTY? WHAT IS THE PROPER AND MOST EFFECTIVE ROLE FOR GOVERNMENT AND NON GOVERNMENT ENTITIES IN CONTROLLING THE POTENTIALLY UNWARRANTED APPLICATION OF SUCH TESTS?
- RECENT REPORTS SUGGEST THAT JOINT VENTURES ARE BEGINNING TO EMERGE BETWEEN U.S. COMPANIES AND JAPANESE FIRMS TO CONDUCT GENETIC SCREENING. ARE SUCH ARRANGEMENTS REGULATED BY THE U.S.? DOES THIS OFFER THE POTENTIAL FOR ANY PROBLEM WITH PREMATURE USE OF SCREENING BEFORE EFFICACY IS ASSURED?

"HUMAN GENOME--ISSUES"
OCTOBER 4, 1994
ADDITIONAL QUESTIONS FOR THE RECORD

PANEL 2 (ISSUES OF SCIENCE AND SOCIAL IMPACT)

- WHAT CAN BE DONE TO IMPROVE THE EFFICIENCY AND PRODUCTIVITY OF THE FEDERAL CONTRIBUTION TO HUMAN GENOME RESEARCH AT DOE LABS AND NIH?
- A SIGNIFICANT AMOUNT OF EFFORT HAS FOCUSED ON THE QUESTION OF ACCESS TO INSURANCE IF AN INDIVIDUAL HAS A GENETICALLY LINKED DISEASE. WITHOUT HEALTH REFORM, WHO WILL MAKE THE DECISIONS FOR GRANTING INSURANCE TO THOSE INDIVIDUALS WITH "PREEXISTING CONDITIONS"? STATE INSURANCE COMMISSIONS?
- THE OFFICE OF SCIENCE AND TECHNOLOGY POLICY HAS RECENTLY PROPOSED A BIOETHICS COMMISSION TO ADDRESS A NUMBER OF ISSUES INCLUDING HUMAN SUBJECT RESEARCH AND GENETIC TESTING. TO WHAT DEGREE WOULD SUCH A COMMISSION REDUCE THE NEED FOR THE CURRENT JOINT NIH-DOE JOINT WORKING GROUP ON ETHICAL, LEGAL AND SOCIAL ISSUES? WHAT IS THE APPROPRIATE ROLE FOR THE JOINT WORKING GROUP IF THE COMMISSION IS ESTABLISHED? WHAT IF IT ISN'T ESTABLISHED? WHAT DO YOU BELIEVE ARE THE SPECIAL STRENGTHS AND LIMITATIONS OF THE ELSI WORKING GROUP IN IDENTIFYING AND ADDRESSING EMERGING POLICY ISSUES RESULTING FROM HUMAN GENOME RESEARCH?
- A RECENT REPORT OF THE INSTITUTE OF MEDICINE FUNDED BY DOE AND NIH NOTED THAT THERE MAY ARISE A CONFLICT OF INTEREST ON THE PART OF THOSE WHO ARE IN A POSITION TO RECOMMEND GENETIC TESTS BECAUSE THEY MAY HAVE A FINANCIAL INTEREST IN LABORATORIES OR COMPANIES THAT PROVIDE TESTING. WHAT IS THE BEST WAY TO DEAL WITH THIS SITUATION?
- FUNDING FOR THE ETHICAL, LEGAL AND SOCIAL ISSUES PROGRAM IS ABOUT 3 PERCENT OF THE DOE RESEARCH PROGRAM AND 5 PERCENT OF THE NIH RESEARCH PROGRAM. IS THERE A RATIONALE

FOR CALCULATING HOW MUCH FUNDING SHOULD BE DEVOTED TO THESE ISSUES? IS 3 TO 5 PERCENT ENOUGH?

- THE EXTENSIVE MEDIA ATTENTION ON THE IMPORTANT GENETIC DISCOVERIES MAY LEAD TO AN IMPRESSION BY THE PUBLIC, THAT NOT ONLY DISEASE, BUT MANY BEHAVIORS CAN BE EXPLAINED BY GENETIC MAKE-UP. WHAT ARE THE STEPS THAT NEED TO BE TAKEN NOW TO ASSURE THAT WE DON'T OVERSELL THE RESEARCH FINDINGS THAT COULD LEAD TO A SIMPLISTIC CONCEPTION OF GENETIC DETERMINISM?

"HUMAN GENOME--ISSUES"

OCTOBER 4, 1994

ADDITIONAL QUESTIONS FOR THE RECORD

Questions for Dr. Holtzman

1. Genetic tests differ from most other medical tests in that they can be offered to people who are healthy in order to predict risk of future disease in themselves or their offspring. Particularly for complex diseases for which there are genetic predispositions, they will not be able to predict everyone who is going to get the diseases. Moreover, some people who have positive test results for such diseases, will never become ill with these diseases.

Several genetic tests are a part of routine care. These include prenatal screening for neural tube defects and Down syndrome; carrier testing in high risk ethnic groups for Tay-Sachs, sickle cell anemia and thalassemia; neonatal screening for phenylketonuria, sickle cell anemia, congenital hypothyroidism (not always genetic), and other rare single-gene disorders. At the present time, there are genetic tests for several hundred, rare, single-gene diseases.

A few states, notably California and New York, have fairly stringent regulations for assuring the quality of genetic tests. As I indicated in my testimony, the Health Care Financing Administration has the authority under the Clinical Laboratory Improvement Amendments of 1988 to regulate the quality of laboratories offering genetic tests. HCFA has not yet enforced the Amendments as they pertain to genetic tests with the possible exception of cytogenetic tests.

No systematic attempt has been made to ascertain the accuracy of information people are receiving. Proficiency studies for certain genetic tests, indicate that laboratories do make mistakes. Studies of newborn screening about 10 years ago show that errors are made in the handling of specimens, laboratory analyses, and communication of the results. Qualitative studies of prenatal genetic testing indicate that some women have an inadequate understanding of the tests or their implications. An individual who receives inaccurate information and who suffers harm, or whose child suffers harm, as a result has recourse to the courts. I cannot say whether this will become a consumer fraud problem, but as the number of genetic tests increases, the number of mistakes will also increase unless policies governing laboratory quality are improved.

2. Largely as a result of the recommendations for improved laboratory quality in the Institute of Medicine's report "Assessing Genetic Risks", the Working Group for Ethical, Legal, and Social Implications (ELSI) of the Human Genome Project has initiated a Task Force on Genetic Testing that will bring together biotechnology and insurance industry representatives

with professional, consumer and government representatives to explore the adequacy of policies for the development and delivery of safe and effective genetic tests and for assuring the quality of laboratories providing those tests. Where needed, the Task Force will make specific recommendations for improving policies. Both FDA and HCFA have acknowledged the need for such a Task Force and will send representatives to the Task Force.

3. If companies marketing genetic tests, and commercial and other laboratories providing tests agreed to, or had to comply with, criteria for offering genetic tests to the public, individuals would have much less "sorting through" to do. It would be appropriate, for instance, to assure that information on the sensitivity and positive predictive value of genetic tests, and on the implications of positive and negative results, be provided to anyone offered genetic testing. Until it is clear that most people understand the nature and implications of genetic tests, the knowledge of key aspects could be ascertained as part of the informed consent process. By bringing government agencies and non-government organizations together, the Task Force on Genetic Testing hopes to reduce the unwarranted application of genetic tests.

4. I do not have the expertise to deal with the implications of international agreements on genetic testing in the United States. It does seem to me that the United States should retain full sovereignty to assure that tests offered in the U.S. are safe and effective and meet American standards when our standards are more stringent than those in other countries.

Panel 2 (Issues of Science and Social Impact)

1. I am not qualified to comment on improving the efficiency and productivity of the federal contribution to human genome research at DOE labs and NIH.

2. Except for self-insured companies, states regulate insurance companies. I do not know, however, whether state commissions could rule on coverage for pre-existing conditions; it might require state legislation. Under ERISA, self-insured employers are exempt from state regulation. A federal law could either return authority to the states or prohibit exclusion from coverage for pre-existing conditions. On a related matter, the Americans with Disabilities Act does not (i) specifically designate genetic predispositions as protected under the Act; (ii) prohibit employers from excluding genetic (or other conditions) from health care benefits. Both of these defects should be rectified.

3. The breadth of issues that should be addressed by a bioethics commission would, I believe preclude it from examining the

ethical, legal, and social implications of the human genome project in the depth that the ELSI Working Group has so far succeeded in doing. I doubt, moreover, that such a commission would have much interest in addressing the laboratory deficiencies that the Committee questioned me about and that the ELSI working group is addressing. The ELSI Working Group has been able to draw together biological, social, and behavioral scientists, philosophers, policy makers, and consumers to address important issues. Its special relationship both to NIH and DOE granting agencies has helped integrate concerns of the Working Group into the grant priorities of both agencies. The Working group has avoided partisan political infighting that might weaken the effectiveness of a high-level commission.

4. I commented on conflict of interest in response to Chairman Lloyd's question. The ideal solution would be to prohibit genetic counselors from having a financial interest in a person having a genetic test. As an important salary source for genetic counselors today is the revenue from testing, this would be difficult to accomplish. Greater reimbursement for counseling per se could rectify the situation. Alternatively, a disclosure of the potential conflict could be part of the informed consent process when a person decides to have a genetic test.

5. I do not know whether 3 to 5 percent is enough. NIH and DOE should be asked to describe the grants that have been approved but never funded and indicate whether they believe that meritorious work is, consequently, not being done.

6. I am greatly concerned that the media's reporting greatly exaggerates the role of genes in disease. Part of the problem is the media's inability to filter the claims of the scientists (and their university's public affairs offices) who report the discoveries. But even when presented objectively, the media often exaggerates. I have proposed that the NCHGR identify a group of scientists and people who are conversant with the ethical, legal, and social implications of genetic research and who would agree to be available to respond to reporters queries when new discoveries are made. An NIH-DOE sponsored conference for scientists and science writers whose goal would be to develop checklist of questions that should be asked when gene discoveries are reported might be helpful. Improving the knowledge of the public about genetics and genetic testing would not only improve the quality of reporting but make the public more aware of the benefits and the limitations of new discoveries.



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November 28, 1994

Ms. Patti Hartle
Subcommittee on Energy
H2-390 Ford House Office Building
Washington, DC 20515

Dear Ms. Hartle,

I am enclosing my responses to the questions as well as the proofread version of my testimony.

Please let me know if there is anything else you would like for me to do.

Sincerely yours,

Ellen Wright Clayton

Ellen Wright Clayton, MD, JD

"HUMAN GENOME--ISSUES"
OCTOBER 4, 1994
ADDITIONAL QUESTIONS FOR THE RECORD

DR. CLAYTON:

- YOUR TESTIMONY TALKS ABOUT THE NEED TO RETAIN CONFIDENTIALITY OF GENETIC INFORMATION TO PROTECT ACCESS TO HEALTH INSURANCE. HOW SIGNIFICANT A CONCERN IS THIS? HOW MANY INSURERS ARE ACTUALLY DENYING INSURANCE ON THE BASIS OF GENETIC INFORMATION? IS THERE COLLECTED STATISTICS AVAILABLE ON THIS ISSUE OR ARE THE CASES COMING TO LIGHT IN AN AD HOC BASIS. IS THERE A NEED TO SET UP BETTER MONITORING?
- YOUR TESTIMONY REFERS TO THE POTENTIAL SOURCES OF GENETIC INFORMATION IN STORED TISSUE SAMPLES CURRENTLY LOCATED AT HOSPITAL LABS. ARE HOSPITAL LABS THE PRIMARY LOCATIONS OR ARE THERE OTHER STORAGE LOCATIONS? TO WHAT DEGREE ARE THESE REPOSITORIES CURRENTLY BEING ACCESSED, AND HOW IS ACCESS TO THESE DATA SOURCES CONDUCTED AND CONTROLLED?
- THE COMMITTEE HAS RAISED CONCERNS IN THE PAST ABOUT THE DEGREE OF PROTECTION FOR INDIVIDUALS WHEN THEY (OR DATA ABOUT THEM) IS USED FOR HUMAN SUBJECT RESEARCH. CAN YOU COMMENT ON THE APPLICABILITY OR EFFICACY OF THE CURRENT HUMAN SUBJECT RESEARCH GUIDELINES TO ADEQUATELY PROTECT INDIVIDUALS FROM UNWARRANTED INVASION OF PRIVACY OR ACTION WITHOUT INFORMED CONSENT

"HUMAN GENOME--ISSUES"
OCTOBER 4, 1994
ADDITIONAL QUESTIONS FOR THE RECORD

PANEL 2 (ISSUES OF SCIENCE AND SOCIAL IMPACT)

- WHAT CAN BE DONE TO IMPROVE THE EFFICIENCY AND PRODUCTIVITY OF THE FEDERAL CONTRIBUTION TO HUMAN GENOME RESEARCH AT DOE LABS AND NIH?
- A SIGNIFICANT AMOUNT OF EFFORT HAS FOCUSED ON THE QUESTION OF ACCESS TO INSURANCE IF AN INDIVIDUAL HAS A GENETICALLY LINKED DISEASE. WITHOUT HEALTH REFORM, WHO WILL MAKE THE DECISIONS FOR GRANTING INSURANCE TO THOSE INDIVIDUALS WITH "PREEXISTING CONDITIONS"? STATE INSURANCE COMMISSIONS?
- THE OFFICE OF SCIENCE AND TECHNOLOGY POLICY HAS RECENTLY PROPOSED A BIOETHICS COMMISSION TO ADDRESS A NUMBER OF ISSUES INCLUDING HUMAN SUBJECT RESEARCH AND GENETIC TESTING. TO WHAT DEGREE WOULD SUCH A COMMISSION REDUCE THE NEED FOR THE CURRENT JOINT NIH-DOE JOINT WORKING GROUP ON ETHICAL, LEGAL AND SOCIAL ISSUES? WHAT IS THE APPROPRIATE ROLE FOR THE JOINT WORKING GROUP IF THE COMMISSION IS ESTABLISHED? WHAT IF IT ISN'T ESTABLISHED? WHAT DO YOU BELIEVE ARE THE SPECIAL STRENGTHS AND LIMITATIONS OF THE ELSI WORKING GROUP IN IDENTIFYING AND ADDRESSING EMERGING POLICY ISSUES RESULTING FROM HUMAN GENOME RESEARCH?
- A RECENT REPORT OF THE INSTITUTE OF MEDICINE FUNDED BY DOE AND NIH NOTED THAT THERE MAY ARISE A CONFLICT OF INTEREST ON THE PART OF THOSE WHO ARE IN A POSITION TO RECOMMEND GENETIC TESTS BECAUSE THEY MAY HAVE A FINANCIAL INTEREST IN LABORATORIES OR COMPANIES THAT PROVIDE TESTING. WHAT IS THE BEST WAY TO DEAL WITH THIS SITUATION?
- FUNDING FOR THE ETHICAL, LEGAL AND SOCIAL ISSUES PROGRAM IS ABOUT 3 PERCENT OF THE DOE RESEARCH PROGRAM AND 5 PERCENT OF THE NIH RESEARCH PROGRAM. IS THERE A RATIONALE

HUMAN GENOME -- ISSUES
U.S. House of Representatives
Committee on Science, Space, and Technology
Responses of Ellen Wright Clayton

Questions directed to Dr. Clayton

I. In response to your questions about insurance, I would direct the committee to the Report of the Task Force on Genetic Information and Insurance, entitled Genetic Information and Health Insurance. In brief, it is very difficult to get an accurate picture of the impact of genetic information on access to health insurance, in part because of the highly fragmented nature of this market and in part because of the difficulty of ascertaining the degree and impact of "job lock" that can result from problems with health insurance. There is need for more aggressive monitoring. Clearly, health insurance is denied or made more expensive if one has a family history of early onset breast cancer or cardiovascular disease, both of which can have significant genetic components. Having a mutation in BRCA1 would probably make it impossible to get health insurance in the private market. It is less clear how frequently being a carrier for a recessive disorder which can affect the health only of one's children has an adverse impact on access to health insurance, but some people have experienced exclusion.

II. Tissue samples are stored in hospital laboratories as well as many other locations. State laboratories keep newborn screening blood spots for varying lengths of time. In addition, some tissue samples are kept in special repositories. There is no uniformity either in degree of access or control. A recent survey of directors of state newborn screening labs revealed widely varying policies with regard to access, including in some instances relatively free access without formal review or consent of the parents. A recent conference held by the National Cancer Institute which was attended by directors of many tissue repositories also demonstrated widely varying policies.

III. I believe that the current regulations, if appropriately applied, largely provide adequate protection for the interests of individuals. The only two revisions that I might make in the regulations are 1) requiring explicitly that psychosocial harms be taken into account, and 2) broadening the shield of confidentiality that institutions and investigators can extend to individuals. My main concern, however, is that the current regulations are not being appropriately applied.

Questions directed to Panel 2

I. I have no opinion on this issue.

II. State insurance commissions regulate far less than half of all health insurance in this country. The overwhelming majority of employees receive health insurance from their employers who

self-insure and so are subject only to ERISA which provides wholly inadequate protection. At the moment, it appears that the most important body of law limiting exclusion for pre-existing conditions is the Americans with Disabilities Act although its protection, too, is incomplete. There is need for sweeping change in this area. Mark Rothstein at the University of Houston, among others, has written extensively on this issue.

III. It is entirely unclear how these two bodies would relate to each other. There should be room and need for both, in that the issues raised by genetics can profitably be considered both in the larger frame that might be the purview of the proposed bioethics commission as well as in a more focused manner that would be the purview of the Working Group. I have not worked closely enough with the Working Group to have an informed opinion about its strengths and weaknesses.

IV. This issue does not differ in any important way from the issues of self-referral that Congress has already been addressing for some time.

V. There is no objective way to determine how many resources ought to be devoted to studying the ethical, legal, and social issues raised by genetics or indeed any other area of medicine. It is, however, desirable to devote more federal resources to these considerations both because it is becoming increasingly clear how important and pervasive these issues are and because the recent changes in the health care environment have made medical schools increasingly unwilling to support individuals who engage in these analyses.

VI. The only responses to genetic determinism are continual reminders that human characteristics are the results of interactions between their genetic makeup and their environments, that the presence of a certain genetic makeup does not necessarily that there is no possibility for assistance, and that we as a society have responsibilities to all our members regardless of our genetic differences.

**HOUSE SCIENCE, SPACE AND TECHNOLOGY COMMITTEE
SUBCOMMITTEE ON ENERGY**

OCTOBER 4, 1994

ADDITIONAL QUESTIONS FOR THE RECORD

**Robyn Y. Nishimi, Ph.D.
Senior Associate
Office of Technology Assessment**

YOUR TESTIMONY NOTES THAT INCREASED GENETICS EDUCATION FOR ALL HEALTH CARE PROFESSIONALS IS DESIRABLE AND WILL BE NECESSARY. WHAT ARE THE VARIOUS ROLES THAT FEDERAL, STATE AND LOCAL ENTITIES CAN PLAY TO ACHIEVE THIS EDUCATIONAL OBJECTIVE?

The federal government provides financial support for education and training of certain health personnel through Title VII and Title VIII of the Public Health Service Act. Title VII provides education support to the fields of medicine, osteopathy, dentistry, veterinary medicine, optometry, podiatry, public health, and graduate programs in health administration. It does so through grants and contracts to institutions, and through loans to individuals. Title VIII focuses primarily on advanced training of nurses. The Maternal and Child Health (MCH) block grant also supports some genetics-related training and education.

Legislation could be enacted that amends Title VII or Title VIII to include master's-level genetic counseling programs. The federal government could also encourage increased genetics education for the other health professions encompassed by these titles. Grantees and contractors that receive Title VII or Title VIII funds, for example, might be required to increase genetics-related curriculum for all health professionals. With respect to the MCH block grant, Congress could stipulate that states receiving MCH funds earmark a designated level of state funds to genetics education, training, or both.

For genetics education for professionals already practicing, Congress could encourage that the Ethical, Legal, and Social Issues (ELSI) programs of the National Institutes of Health (NIH) and the Department of Energy (DoE) increase the proportion of grants devoted to continuing genetics education of health care professionals. Similarly, Congress could direct that professional training and continuing education be emphasized under the MCH block grant.

State and local entities could facilitate genetics education of health professionals by devoting state or local resources to this purpose. A state also could opt to allot a greater share of its MCH block grant for genetics education and training.

YOUR TESTIMONY NOTES THAT ONE OF THE MOST SENSITIVE ISSUES IS EMPLOYMENT AND POSSIBLE DISCRIMINATION IN THE WORKPLACE. DO WE HAVE AN ADEQUATE POLICY MECHANISM IN PLACE TO ADDRESS THESE ISSUES? WHAT ROLE WOULD THE PROPOSED NATIONAL BIOETHICS COMMISSION PLAY IN RESOLVING THESE ISSUES?

Recent concern about genetic discrimination has focused on the applicability of the Americans With Disabilities Act (ADA) to genetic disorders and genetic predispositions. As enacted, the ADA left open the question of whether genetic predisposition to illness or carrier status were covered as protected classes. In its final rule, the Equal Employment

Opportunity Commission (EEOC) rejected the premise that genetic predisposition or carrier status are covered under the ADA for employment purposes. Because some debate exists as to the intent of Congress in this area, Congress could revisit the issue to clarify its intentions with respect to genetic and disability discrimination under the ADA.

Additionally, the ADA is silent on whether employers may discriminate--for the purposes of hiring--against individuals who are perceived as more likely to incur extra costs (e.g., CF carriers) due to illnesses that could occur in their future children. A 1989 OTA survey of Fortune 500 companies and companies with 1,000 or more employees revealed that 9 percent of employers surveyed account for dependents' potential expenses when considering an individual's job application. If Congress determines the potential health insurance costs of an applicant's dependent should not be considered in hiring decisions, it could signal its intent through legislation.

The OTA reports *Genetic Monitoring and Screening in the Workplace* and *Cystic Fibrosis and DNA Tests: Implications of Carrier Screening* discuss these issues in greater detail.

Regarding the role of the proposed National Bioethics Advisory Commission (NBAC), the draft charter states that "as a first priority, the Commission will direct its attention to consideration of issues in the management and use of genetic information." It appears that NBAC could decide that employment and/or discrimination issues fall within the scope of this language.

WHAT DO YOU SEE AS THE PARTICULAR STRENGTHS AND LIMITATIONS OF THE PROPOSED COMMISSION BASED ON OTA'S PRIOR STUDIES?

OTA's analysis of bioethics commissions in our report, *Biomedical Ethics in U.S. Public Policy*, identified six primary factors that contribute to the success or failure of an effort. They are: budget, including staffing; mandate and flexibility to control the agenda; appointment process; bureaucratic location; target audiences; and reporting and response requirements. The proposed NBAC charter addresses each of these factors.

The provision that has drawn the most attention is in the area of NBAC's mandate. As currently proposed, NBAC would embark on studies in consultation with the President's National Science and Technology Council (NSTC). Concern has been raised by congressional and non-congressional parties that, structurally speaking, such a close linkage to the NSTC is less preferable than a free-standing, independent body like the President's Commission for the Study of Ethical Problems in Medicine and Biomedical and Behavioral Research.

TO WHAT EXTENT ARE THE SOCIAL AND ETHICAL ISSUES RELATED TO DNA BEING DISCUSSED AND DEBATED AT PUBLIC MEETINGS AND SEMINARS? HAVE YOU ATTENDED ANY OF THESE MEETINGS? WHAT IS THEIR QUALITY?

Both DoE and NIH have supported various conferences on the ethical, legal, and social issues of the Human Genome Project. Additionally, the National Center for Human Genome research has a seminar series on aspects of the Human Genome Project; these talks are open to the public. Public forums on the ethical, legal and social issues are also held in conjunction with scientific meetings related to human genetics.

I have attended many of these meetings. Not surprisingly, some are better than others, and it is impossible to make any generalized statement.

WHAT CAN BE DONE TO IMPROVE THE EFFICIENCY AND PRODUCTIVITY OF THE FEDERAL CONTRIBUTION TO HUMAN GENOME RESEARCH AT DOE LABS AND NIH?

OTA has not analyzed the intramural genome programs of DoE or NIH and so cannot comment on their efficiency and productivity.

A SIGNIFICANT AMOUNT OF EFFORT HAS FOCUSED ON THE QUESTION OF ACCESS TO INSURANCE IF AN INDIVIDUAL HAS A GENETICALLY LINKED DISEASE. WITHOUT HEALTH REFORM, WHO WILL MAKE THE DECISIONS FOR GRANTING INSURANCE TO THOSE INDIVIDUALS WITH "PREEXISTING CONDITIONS"? STATE INSURANCE COMMISSIONS?

The extent to which genetic preexisting conditions affect the ability to secure health insurance largely centers on individual policies or medically underwritten small group policies. Hence, decisions on eligibility will be made on a carrier by carrier and individual by individual basis, although state insurance commissions could step in to regulate all policies under its jurisdiction.

In some cases, employers can make decisions related to covering preexisting conditions. That is, employers who offer health insurance through ERISA-based, self-funded plans can cap, modify, or eliminate health care benefits for a particular condition at any time, as long as the company complies with notification requirements. ERISA would preempt any state law related to genetically linked disease and preexisting conditions.

THE OFFICE OF SCIENCE AND TECHNOLOGY POLICY HAS RECENTLY PROPOSED A BIOETHICS COMMISSION TO ADDRESS A NUMBER OF ISSUES INCLUDING HUMAN SUBJECT RESEARCH AND GENETIC TESTING. TO WHAT DEGREE WOULD SUCH A COMMISSION REDUCE THE NEED FOR THE CURRENT JOINT NIH-DOE WORKING GROUP ON ETHICAL, LEGAL, AND SOCIAL ISSUES? WHAT IS THE APPROPRIATE ROLE FOR THE JOINT WORKING GROUP IS THE COMMISSION IS ESTABLISHED? WHAT IF IT ISN'T ESTABLISHED? WHAT DO YOU BELIEVE ARE THE SPECIAL STRENGTHS AND LIMITATIONS OF THE ELSI WORKING GROUP IN IDENTIFYING AND ADDRESSING EMERGING POLICY ISSUES RESULTING FROM HUMAN GENOME RESEARCH?

As I have indicated in my written testimony, the ELSI programs fund research related to the Human Genome Project in order to expand the knowledge base in the broad area of genetics and ethics, law, and social and public policies. The programs operate independently in the model of peer review competition for grant funds. The ELSI Working group, which is a joint NIH-DOE effort, advises both programs; initially, it framed the agenda and established priority research areas.

The nature of grant programs means the ultimate direction largely evolves from the bottom up--i.e., from the individual perspectives of researchers pursuing independent investigations--rather than from the top down--i.e., through policymakers or an overarching federal body. Furthermore, no formal mechanism exists for ELSI-funded research findings to directly make their way back into the policy process.

Despite the recommendation of at least two successive Congresses that the National Center for Human Genome Research (NCHGR) adopt a commission-like mechanism with adequate staffing to examine and implement guidelines or recommendations derived from its ELSI grant portfolio, no such entity has materialized. In the past few months, however, NCHGR has moved to expand its policy analysis capacity. Thus, the extent to

which any implementation of ELSI Working Group recommendations moves forward is currently in flux.

NBAC, if constituted, could provide a high profile, cross-agency forum to address some issues pertinent to the Human Genome Project. For example, the draft charter includes the direction that, "as a first priority, the Commission will direct its attention to consideration of issues in the management and use of genetic information," such a study is only one of two directly identified as NBAC topics. Moreover, NBAC recommendations may carry significant weight by virtue of the position the commission occupies in the executive hierarchy.

Additionally, the draft charter contains language that compels departments and agencies to respond to any NBAC recommendations. The draft NBAC charter states that "[t]he Commission may specifically identify the Federal department, agency or other entity to which particular recommendations are directed and request a response from the Federal department, agency or other entity within 180 days of publication of such recommendations." In other words, should the agency opt not to implement an NBAC recommendation, the agency must publish public notice that details the reasons it is not doing so. OTA found such a "forcing clause" to be an important factor in the effectiveness of past bioethics commissions. In contrast, such authority is not held by the ELSI Working Group.

Still, NBAC clearly is positioned to undertake work that is of policy interest to multiple agencies; such an authority and purpose is expressly stated in the draft charter. Thus, some items important to policy analysis and implementation related to the Human Genome Project might be viewed as too narrow for NBAC to undertake. Hence, it will be important to examine the relationship between NBAC, the ELSI Working Group, and NCHGR's intramural policy analysis capacity. Because none of the entities is in place in its likely future form, however, it is not possible for OTA to speculate further about how this landscape will shape up.

A RECENT REPORT OF THE INSTITUTE OF MEDICINE FUNDED BY DOE AND NIH NOTED THAT THERE MAY ARISE A CONFLICT OF INTEREST ON THE PART OF THOSE WHO ARE IN A POSITION TO RECOMMEND GENETIC TESTS BECAUSE THEY MAY HAVE A FINANCIAL INTEREST IN LABORATORIES OR COMPANIES THAT PROVIDE TESTING. WHAT IS THE BEST WAY TO DEAL WITH THIS SITUATION?

OTA has not evaluated the issue of conflict of interest for providers of genetic services who might also have a fiduciary interest in the laboratories or companies that perform the tests.

FUNDING FOR THE ETHICAL, LEGAL, AND SOCIAL ISSUES PROGRAM IS ABOUT 3 PERCENT OF THE DOE RESEARCH PROGRAM AND 5 PERCENT OF THE NIH RESEARCH PROGRAM. IS THERE A RATIONALE FOR CALCULATING HOW MUCH FUNDING SHOULD BE DEVOTED TO THIS ISSUES? IS 3 TO 5 PERCENT ENOUGH?

OTA unaware of any analyses that present the rationale for the current funding levels for the ELSI programs or whether the percent allocations are adequate, inadequate, or too much.

THE EXTENSIVE MEDIA ATTENTION ON THE IMPORTANT GENETIC DISCOVERIES MAY LEAD TO AN IMPRESSION BY THE PUBLIC THAT NOT ONLY DISEASE, BUT MANY BEHAVIORS CAN BE EXPLAINED BY GENETIC MAKE-UP. WHAT ARE THE STEPS THAT NEED TO BE TAKEN NOW TO ASSURE THAT WE DON'T OVERSELL THE RESEARCH FINDINGS THAT COULD LEAD TO A SIMPLISTIC CONCEPTION OF GENETIC DETERMINISM.

As my statement indicates, public education about the benefits and risks--medical and social--of genetics is paramount. Public understanding of the scientific, technical, ethical, social, and legal implications of the growing body of genetic information is absolutely necessary for the wise and thoughtful application of this knowledge.



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